TITLE OF THE INVENTION

OPHTHALMIC COMPOSITIONS FOR TREATING OCULAR HYPERTENSION

This application claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application No. 60/499,628 filed 9/2/2003.

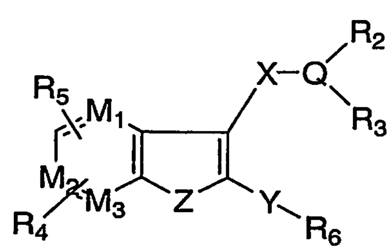
BACKGROUND OF THE INVENTION

Glaucoma is a degenerative disease of the eye wherein the intraocular pressure is too high to permit normal eye function. As a result, damage may occur to the optic nerve head and result in irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects, is now believed by the majority of ophthalmologists to represent merely the earliest phase in the onset of glaucoma.

There are several therapies for treating glaucoma and elevated intraocular pressure, but the efficacy and the side effect profiles of these agents are not ideal. Recently potassium channel blockers were found to reduce intraocular pressure in the eye and therefore provide yet one more approach to the treatment of ocular hypertension and the degenerative ocular conditions related thereto. Blockage of potassium channels can diminish fluid secretion, and under some circumstances, increase smooth muscle contraction and would be expected to lower IOP and have neuroprotective effects in the eye. (see US Patent Nos. 5,573,758 and 5,925,342; Moore, et al., Invest. Ophthalmol. Vis. Sci 38, 1997; WO 89/10757, WO94/28900, and WO 96/33719).

SUMMARY OF THE INVENTION

This invention relates to the use of potent potassium channel blockers or a formulation thereof in the treatment of glaucoma and other conditions that are related to elevated intraocular pressure in the eye of a patient. This invention also relates to the use of such compounds to provide a neuroprotective effect to the eye of mammalian species, particularly humans. More particularly this invention relates to the treatment of glaucoma and/or ocular hypertension (elevated intraocular pressure) using novel benzofurans, benzothiophenes, and their aza derivatives having the structural formula I:



where

Formula I

or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof:
wherein,

R represents hydrogen, or C_{1-6} alkyl;

X represents $-(CHR_7)_p-$, or $-(CHR_7)_pCO-$;

Y represents $-CO(CH_2)_n-$, $(CH_2)_n$, $-CH(OR)-$, OR_6, or SR_6;

Z=O or S;

M1, M2, and M3 are independently CH or N;

Q represents CR^y, N, or O, wherein R_2 is absent when Q is O;

R^y represents H, C_{1-6} alkyl, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-(CH_2)_nC_{5-10}$ heteroaryl, or $-(CH_2)_nC_{6-10}$ aryl;

R_w represents H, C_{1-6} alkyl, $-C(O)C_{1-6}$ alkyl, $-C(O)OC_{1-6}$ alkyl, $-SO_2N(R)_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2C_{6-10}$ aryl, NO_2, CN or $-C(O)N(R)_2$;

R_2 represents hydrogen, C_{1-10} alkyl, OH, C_{2-6} alkenyl, C_{1-6} alkylSR, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{1-6}$ alkoxy, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{3-8}$ cycloalkyl, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{3-8}$cycloalkenyl, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{3-10}$ heterocyclyl, $-N(R)_2$, $-COOR$, or $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{6-10}$ aryl, said alkyl, cycloalkyl, heterocyclyl, or aryl optionally substituted with 1-5 groups selected from R^a;

R_3 represents hydrogen, C_{1-10} alkyl, C_{2-6} alkenyl, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{3-8}$ cycloalkyl, $-(CH_2)_n(CHR_7)_q(CH_2)_m$cycloalkenyl, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{3-10}$ heterocyclyl, $-(CH_2)_n(CHR_7)_q(CH_2)_mCOOR$, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{6-10}$ aryl, $-(CH_2)_n(CHR_7)_q(CH_2)_mNHR_8$, $-(CH_2)_n(CHR_7)_q(CH_2)_mN(R)_2$, $-(CH_2)_n(CHR_7)_q(CH_2)_mN(R)_3$, $-(CH_2)_n(CHR_7)_q(CH_2)_mN(R_8)_2$, $-(CH_2)_n(CHR_7)_q(CH_2)_mNHCOOR$, $-(CH_2)_n(CHR_7)_q(CH_2)_mN(R_8)CO_2R$, $-(CH_2)_n(CHR_7)_q(CH_2)_mN(R_8)COR$, $-(CH_2)_n(CHR_7)_q(CH_2)_mNHCOR$, -

$(CH_2)_n(CHR_7)_q(CH_2)_mCONH(R_8)$, aryl, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{1-6}$ alkoxy, CF_3, $-(CH_2)_n(CHR_7)_q(CH_2)_mSO_2R$, $-(CH_2)_n(CHR_7)_q(CH_2)_mSO_2N(R)_2$, $-(CH_2)_n(CHR_7)_q(CH_2)_mCON(R)_2$, $-(CH_2)_n(CHR_7)_q(CH_2)_mCONHC(R)_3$, $-(CH_2)_n(CHR_7)_q(CH_2)_mCONHC(R)_2CO_2R$, $-(CH_2)_n(CHR_7)_q(CH_2)_mCOR_8$, nitro, cyano or halogen, said alkyl, cycloalkyl, alkoxy, heterocyclyl, or aryl optionally substituted with 1-5 groups of R^a;

or, when Q equals CR^y or N, R_2 and R_3 taken together with the intervening CR^y or N form a 3-10 membered carbocyclic or heterocyclic ring or fused ring optionally interrupted by 1-2 atoms of O, S, C(O) or NR, and optionally having 1-5 double bonds, and optionally substituted by 1-3 groups selected from R^a;

R_4 and R_5 independently represent hydrogen, C_{1-6} alkoxy, OH, C_{1-6} alkyl, C_{1-6} alkyl-S, C_{1-6} alkyl-CO-, C_{1-6} alkenyl, C_{3-8} cycloalkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-S, C_{3-8} cycloalkyl-CO-, COOR, SO_3H, $-O(CH_2)_nN(R)_2$, $-O(CH_2)_nCO_2R$, $-OPO(OH)_2$, CF_3, $-N(R)_2$, nitro, cyano, C_{1-6} alkylamino, or halogen;

R_6 represents hydrogen, C_{1-10} alkyl, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{6-10}$ aryl, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{5-10}$ heteroaryl, NR_cR_d, $-NR-(CH_2)_n(CHR_7)_q(CH_2)_mC_{6-10}$ aryl, $-N-((CH_2)_n(CHR_7)_q(CH_2)_mC_{6-10}\text{ aryl})_2$, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{3-10}$ heterocyclyl, $-NR-(CH_2)_n(CHR_7)_q(CH_2)_mC_{3-10}$ heterocyclyl, $-N-((CH_2)_n(CHR_7)_q(CH_2)_mC_{3-10}\text{ heterocyclyl})_2$ $(C_{6-10}\text{ aryl})O-$, $-(CH_2)_n(CHR_7)_q(CH_2)_mC_{3-8}$ cycloalkyl, -COOR, $-C(O)CO_2R$, said aryl, cycloalkyl, heteroaryl, heterocyclyl and alkyl optionally substituted with 1-3 groups selected from R^a;

R_c and R_d independently represent H, C1-6 alkyl, C_{2-6} alkenyl, $-(CH_2)_nC_{6-10}$ aryl, $-(CH_2)_nC_{5-10}$ heteroaryl, C_{1-6} alkylSR, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, or $-(CH_2)_nC_{3-8}$ cycloalkyl;

or R_c and R_d taken together with the intervening N atom form a 4-10 membered heterocyclic carbon ring optionally interrupted by 1-2 atoms of O, S, C(O) or NR, and optionally having 1-4 double bonds, and optionally substituted by 1-3 groups selected from R^a;

R_7 represents hydrogen, C_{1-6} alkyl, $-(CH_2)_nCOOR$ or $-(CH_2)_nN(R)_2$,

R_8 represents $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_n$ 3-10 heterocyclyl, C_{1-6} alkoxy or $-(CH_2)_nC_{5-10}$ heteroaryl, $-(CH_2)_nC_{6-10}$ aryl said cycloalkyl, heterocyclyl, aryl or heteroaryl optionally substituted with 1-3 groups selected from R^a;

R^a represents F, Cl, Br, I, CF_3, $N(R)_2$, NO_2, CN, $-COR_8$, $-CONHR_8$, $-CON(R_8)_2$, $-O(CH_2)_nCOOR$, $-NH(CH_2)_nOR$, -COOR, $-OCF_3$, -NHCOR, $-SO_2R$, $-SO_2NR_2$, -SR, (C_1-C_6 alkyl)O-, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, (aryl)O-, -OH, (C_1-C_6 alkyl)$S(O)_m$-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)NH-, -(C_1-C_6 alkyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)-C_{3-10} heterocyclyl-R_w, $-(CH_2)_n-Z^1-C(=Z^2)N(R)_2$, -($C_{2-6}$ alkenyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)-C_{3-10} heterocyclyl-R_w, -(C_{2-6} alkenyl)-Z^1-$C(=Z^2)N(R)_2$, $-(CH_2)_nSO_2R$, $-(CH_2)_nSO_3H$, $-(CH_2)_nPO(OR)_2$, $-(CH_2)_nOH$, $-(CH_2)_n(CHR_7)_q(CH_2)_mOPO(OR)_2$, C_{3-10}cycloalkyl, C_{6-10} aryl, C_{3-10} heterocyclyl, C_{2-6} alkenyl, and C_1-C_{10} alkyl, said alkyl, alkenyl, alkoxy, heterocyclyl and aryl optionally substituted with 1-3 groups selected from C_1-C_6 alkyl, CN, NO_2, $-(CH_2)_nOH$, $-(CH_2)_nOPO(OR)_2$, $CON(R)_2$ and COOR;

Z^1 and Z^2 independently represents NR_w, O, CH_2, or S;

m is 0-3;
n is 0-3;
p is 0-3 and
q is 0-1.

This and other aspects of the invention will be realized upon inspection of the invention as a whole.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to novel potassium channel blockers of Formula I. It also relates to a method for decreasing elevated intraocular pressure or treating glaucoma by administration, preferably topical or intra-camaral administration, of a composition containing a potassium channel blocker of Formula I described hereinabove and a pharmaceutically acceptable carrier. Use of a compound of formula I in claim 1 for the manufacture of a medicament for the treatment of ocular hypertension or glaucoma.

One embodiment of this invention is realized when Y is $-CO(CH_2)_n$ and all other variables are as originally described. A subembodiment of this invention is realized when n is 0.

One embodiment of this invention is realized when Q is -N- and all other variables are as originally described. A subembodiment of this invention is realized when R_2 is C_{1-10} alkyl and R_3 is C_{1-10} alkyl and said alkyl optionally substituted with 1 to 3 groups of R^a.

Another embodiment is realized when Q equals CR^y or N, and R_2 and R_3 taken together with the intervening CR^y or N form a 3-10 membered carbocyclic or heterocyclic ring or fused ring optionally interrupted by 1-2 atoms of O, S, C(O) or NR, and optionally having 1-5 double bonds, and optionally substituted by 1-3 groups selected from R^a;

Another embodiment of this invention is realized when Y is CH(OR) and all other variables are as originally described.

In another embodiment R_w is selected from H, C_{1-6} alkyl, -C(O)C_{1-6} alkyl and -C(O)N(R)$_2$ and all other variables are as originally described..

In another embodiment X is $-(CHR_7)_p-$, p is 1-3 and all other variables are as originally described.

In another embodiment X is $-(CHR_7)_pCO-$, p is 1-3 and all other variables are as originally described.

In another embodiment Z is S and all other variables are as originally described.

In another embodiment Z is O and all other variables are as originally described.

In another embodiment one of R_4 and R_5 is H and the other is C_{1-6} alkoxy, halo or hydrogen.

Another embodiment of this invention is realized when M1, M2, and M3 are CH and all other variables are as originally described.

Another embodiment of this invention is realized when at least one of M1, M2, and M3 is N and the other(s) is CH and all other variables are as originally described.

Still another embodiment of this invention is realized when R_6 is C_{1-6} alkyl, $(CH_2)_nC_{6-10}$ aryl, $(CH_2)_nC_{3-10}$ heterocyclyl, NR_cR_d or $(CH_2)_nC_{3-8}$ cycloalkyl, said alkyl, aryl, heterocyclyl and cycloalkyl optionally substituted with 1 to 5 groups of R^a, and all other variables are as originally described.

Yet another embodiment of this invention is realized when R_6 is $(CH_2)_nC_{6-10}$ aryl, NR_cR_d, or $(CH_2)_nC_{3-10}$ heterocyclyl, said aryl, and heterocyclyl optionally substituted with 1 to 5 groups of R^a, and all other variables are as originally described.

Yet another embodiment of this invention is realized when R_7 is hydrogen or C_{1-6} alkyl, and all other variables are as originally described.

Still another embodiment of this invention is realized when Y is $-CO(CH_2)_n$, Q is –N-, R_2 is C_{1-10} alkyl or C_{1-6} alkylOH and R_3 is C_{1-10} alkyl and said alkyl optionally substituted with

1 to 5 groups of R^a. A sub-embodiment of this invention is realized when n is 0 and Z is O. Another sub-embodiment of this invention is realized when n is 0 and Z is S.

Still another embodiment of this invention is realized when Y is -CO(CH_2)$_n$, Q is CRy, R_2 is C_{1-10} alkyl or C_{1-6} alkylOH and R_3 is C_{1-10} alkyl and said alkyl optionally substituted with 1 to 5 groups of R^a. A sub-embodiment of this invention is realized when n is 0 and Z is O. Another sub-embodiment of this invention is realized when n is 0 and Z is S.

Still another embodiment of this invention is realized when Y is -CO(CH_2)$_n$, Q is O, R_2 is absent and R_3 is C_{1-10} alkyl and said alkyl optionally substituted with 1 to 5 groups of R^a. A subembodiment of this invention is realized when n is 0.

Still another embodiment of this invention is realized when Q is –N-, Y is –CO(CH_2)$_n$, n=0, Z is S, and R_6 is C_{1-6} alkyl, (CH_2)$_n$$C_{6-10}$ aryl, (CH_2)$_n$$C_{5-10}$ heteroaryl, (CH_2)$_n$$C_{3-10}$ heterocyclyl, NR_cR_d or (CH_2)$_n$$C_{3-8}$ cycloalkyl, said alkyl, aryl, heteroaryl, heterocyclyl and alkyl optionally substituted with 1 to 3 groups of R^a. A sub-embodiment of this invention is realized when M1, M2 and M3 are CH, X is –(CHR_7)$_p$CO-, p is 1-3 , R_2 is C_{1-10} alkyl or C_{1-6} alkylOH and R_3 is (CH_2)$_n$$C_{3-10}$ heterocyclyl, said heterocyclyl and alkyl optionally substituted with 1 to 3 groups of R^a.

Still another embodiment of this invention is realized when Q is –CRy-, n=0, Z is S, and R_6 is C_{1-6} alkyl, (CH_2)$_n$$C_{6-10}$ aryl, (CH_2)$_n$$C_{5-10}$ heteroaryl, (CH_2)$_n$$C_{3-10}$ heterocyclyl, NR_cR_d or (CH_2)$_n$$C_{3-8}$ cycloalkyl, said alkyl, aryl, heteroaryl, heterocyclyl and alkyl optionally substituted with 1 to 3 groups of R^a.

Still another embodiment of this invention is realized when Q is –N-, Y is –CO(CH_2)$_n$, n=0, Z is O, and R_6 is C_{1-6} alkyl, (CH_2)$_n$$C_{6-10}$ aryl, (CH_2)$_n$$C_{5-10}$ heteroaryl, (CH_2)$_n$$C_{3-10}$ heterocyclyl, NR_cR_d or (CH_2)$_n$$C_{3-8}$ cycloalkyl, said alkyl, aryl, heteroaryl, heterocyclyl and alkyl optionally substituted with 1 to 3 groups of R^a. A sub-embodiment of this invention is realized when M1, M2 and M3 are CH, X is –(CHR_7)$_p$CO-, p is 1-3 , R_2 is C_{1-10} alkyl or C_{1-6} alkylOH and R_3 is (CH_2)$_n$$C_{3-10}$ heterocyclyl, said heterocyclyl and alkyl optionally substituted with 1 to 3 groups of R^a.

Still another embodiment of this invention is realized when Q is –CRy-, n=0, Z is O, and R_6 is C_{1-6} alkyl, (CH_2)$_n$$C_{6-10}$ aryl, (CH_2)$_n$$C_{5-10}$ heteroaryl, (CH_2)$_n$$C_{3-10}$ heterocyclyl, NR_cR_d or (CH_2)$_n$$C_{3-8}$ cycloalkyl, said alkyl, aryl, heteroaryl, heterocyclyl and alkyl optionally substituted with 1 to 3 groups of R^a.

Another embodiment of this invention is realized when there is a free hydroxyl group in the compound of formula I. A subembodiment of this invention is realized when the hydroxyl group is derivatized to give a phosphate group: -OPO$(OH)_2$.

Another embodiment of the instant invention is realized when R^a is selected from F, Cl, Br, I, CF_3, N$(R)_2$, NO_2, CN, -CONHR_8, -CON$(R_8)_2$, -O(CH_2)$_n$COOR, -NH(CH_2)$_n$OR, -COOR, -OCF_3, -NHCOR, -SO_2R, -SO_2NR_2, -SR, (C_1-C_6 alkyl)O-, -(CH_2)$_n$O(CH_2)$_m$OR, -(CH_2)$_n$$C_{1-6}$ alkoxy,

(aryl)O-, -OH, (C_1-C_6 alkyl)S(O)$_m$-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)NH-, (CH_2)$_n$$C_{3-10}$ heterocyclyl, -(C_1-C_6 alkyl)NR$_w$(CH_2)$_n$$C_{3-10}$ heterocyclyl-R$_w$, -(CH_2)$_n$-Z^1-C(=Z^2)N(R)$_2$, -(C_{2-6} alkenyl)NR$_w$(CH_2)$_n$$C_{3-10}$ heterocyclyl-R$_w$,-(C_{2-6} alkenyl)-Z^1-C(=Z^2)N(R)$_2$,-(CH_2)$_n$$SO_2$R, -($CH_2$)$_n$$SO_3$H, -($CH_2$)$_n$OPO(OR)$_2$, C_{2-6} alkenyl, and C_1-C_{10} alkyl, said alkyl, heterocyclyl and alkenyl, optionally substituted with 1-3 groups selected from C_1-C_6 alkyl, and COOR;

Examples of compounds to be used in this invention are as follows:

N,*N*-Bibutyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetamide,
2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*,*N*-diisobutylacetamide ,
N-(Cyclopropylmethyl)-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-propylacetamide,
N-Cyclohexyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-ethylacetamide,
2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*,*N*-dipropylacetamide,
N-Butyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-ethylacetamide,
2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*,*N*-bis(3-methylbutyl)acetamide,
2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-ethyl-*N*-(3-methylbutyl)acetamide,
N-Butyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-propylacetamide,
1-{5-Methoxy-3-[2-(trans-octahydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]-1-benzofuran-2-yl}-2,2-dimethylpropan-1-one,
1-{5-Methoxy-3-[2-(cis-octahydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]-1-benzofuran-2-yl}-2,2-dimethylpropan-1-one,
1-(3-{2-[Trans-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-5-methoxy-1-benzofuran-2-yl)-2,2-dimethylpropan-1-one,
1-(3-{2-[Cis-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-5-methoxy-1-benzofuran-2-yl)-2,2-dimethylpropan-1-one,
N-(3,3-Dimethylbutyl)-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetamide,
N-(3,3-Dimethylbutyl)-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-ethylacetamide,
1-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-3,3-dimethylbutan-2-one,
2-(2-Benzoyl-5-methoxy-1-benzofuran-3-yl)-*N*,*N*-dibutylacetamide,
1-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-3,3-dimethylpentan-2-one
2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-*N*,*N*-di-n-butylacetamide;
2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-*N*,*N*-diisobutylacetamide;
N-(cyclopropylmethyl)-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-*N*-propylacetamide;
N-cyclohexyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-*N*-ethylacetamide;
2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-*N*,*N*-dipropylacetamide;
N-butyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-*N*-ethylacetamide;
2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-*N*-ethyl-*N*-(3-methylbutyl)acetamide;

N-butyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-*N*-propylacetamide;
2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-*N*,*N*-bis(3-methylbutyl)acetamide;
1-{5-methoxy-3-[2-(trans-octahydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]-1-benzothien-2-yl}-2,2-dimethylpropan-1-one;
1-{5-methoxy-3-[2-(cis-octahydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]-1-benzothien-2-yl}-2,2-dimethylpropan-1-one;
1-(3-{2-[(trans-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-5-methoxy-1-benzothien-2-yl)-2,2-dimethylpropan-1-one;
1-(3-{2-[(cis-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-5-methoxy-1-benzothien-2-yl)-2,2-dimethylpropan-1-one;
N-(3,3-dimethylbutyl)-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-*N*-ethylacetamide;
1-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-3,3-dimethylbutan-2-one;
N-Butyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-methylacetamide;
2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-methyl-*N*-(3-methylbutyl)acetamide;
2-[2-(2,2-dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]-*N*,*N*-di-n-butylacetamide;
2-[2-(2,2-dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]-*N*,*N*-diisobutylacetamide;
N-(cyclopropylmethyl)-2-[2-(2,2-dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]-*N*-propylacetamide;
N-cyclohexyl-2-[2-(2,2-dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]-*N*-ethylacetamide;
2-[2-(2,2-dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]-*N*,*N*-dipropylacetamide;
N-butyl-2-[2-(2,2-dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]-*N*-ethylacetamide;
2-[2-(2,2-dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]-*N*-ethyl-*N*-(3-methylbutyl)acetamide;
N-butyl-2-[2-(2,2-dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]-*N*-propylacetamide;
2-[2-(2,2-dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]-*N*,*N*-bis(3-methylbutyl)acetamide;
1-{5-fluoro-3-[2-(trans-octahydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]-1-benzothien-2-yl}-2,2-dimethylpropan-1-one;
1-{5-fluoro-3-[2-(cis-octahydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]-1-benzothien-2-yl}-2,2-dimethylpropan-1-one;
1-(3-{2-[(trans-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-5-fluoro-1-benzothien-2-yl)-2,2-dimethylpropan-1-one;
1-(3-{2-[(cis-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-5-fluoro-1-benzothien-2-yl)-2,2-dimethylpropan-1-one;
N-(3,3-dimethylbutyl)-2-[2-(2,2-dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]-*N*-ethylacetamide;
2-[2-(2,2-dimethylpropanoyl)-1-benzothien-3-yl]-*N*,*N*-di-n-butylacetamide;
2-[2-(2,2-dimethylpropanoyl)-1-benzothien-3-yl]-*N*,*N*-diisobutylacetamide;
N-(cyclopropylmethyl)-2-[2-(2,2-dimethylpropanoyl)-1-benzothien-3-yl]-*N*-propylacetamide;

N-cyclohexyl-2-[2-(2,2-dimethylpropanoyl)-1-benzothien-3-yl]-*N*-ethylacetamide;
2-[2-(2,2-dimethylpropanoyl)-1-benzothien-3-yl]-*N*,*N*-dipropylacetamide;
N-butyl-2-[2-(2,2-dimethylpropanoyl)-1-benzothien-3-yl]-*N*-ethylacetamide;
2-[2-(2,2-dimethylpropanoyl)-1-benzothien-3-yl]-*N*-ethyl-*N*-(3-methylbutyl)acetamide;
N-butyl-2-[2-(2,2-dimethylpropanoyl)-1-benzothien-3-yl]-*N*-propylacetamide;
2-[2-(2,2-dimethylpropanoyl)-1-benzothien-3-yl]-*N*,*N*-bis(3-methylbutyl)acetamide;
1-{3-[2-(trans-octahydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]-1-benzothien-2-yl}-2,2-dimethylpropan-1-one;
1-{3-[2-(cis-octahydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]-1-benzothien-2-yl}-2,2-dimethylpropan-1-one;
1-(3-{2-[(trans-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-1-benzothien-2-yl)-2,2-dimethylpropan-1-one;
1-(3-{2-[(cis-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-1-benzothien-2-yl)-2,2-dimethylpropan-1-one;
N-(3,3-dimethylbutyl)-2-[2-(2,2-dimethylpropanoyl)-1-benzothien-3-yl]-*N*-ethylacetamide;
or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof.

The invention is described herein in detail using the terms defined below unless otherwise specified.

The compounds of the present invention may have asymmetric centers, chiral axes and chiral planes, and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. (See E.L. Eliel and S.H. Wilen *Stereochemistry of Carbon Compounds* (John Wiley and Sons, New York 1994), in particular pages 1119-1190)

When any variable (e.g. aryl, heterocycle, R^1, R^6 etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 10 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, cyclopropyl cyclopentyl and cyclohexyl. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group".

Cycloalkyl is a cyclic specie of alkyl containing from 3 to 15 carbon atoms, unless otherwise defined, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings, which are fused. Examples of such cycloalkyl elements include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Alkenyl is C_2-C_6 alkenyl.

Alkoxy refers to an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, with the alkyl group optionally substituted as described herein. Said groups are those groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

Halogen (halo) refers to chlorine, fluorine, iodine or bromine.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and the like, as well as rings which are fused, e.g., naphthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. Examples of aryl groups are phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl and phenanthrenyl, preferably phenyl, naphthyl or phenanthrenyl. Aryl groups may likewise be substituted as defined. Preferred substituted aryls include phenyl and naphthyl.

The term heterocyclyl or heterocyclic, as used herein, represents a stable 3- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. The term heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydropyrrolyl, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl. Preferably, heterocycle is selected from 2-azepinonyl, benzimidazolyl, 2-diazapinonyl, dihydroimidazolyl, dihydropyrrolyl, imidazolyl, 2-imidazolidinonyl, indolyl, isoquinolinyl, morpholinyl, piperidyl,

piperazinyl, pyridyl, pyrrolidinyl, 2-piperidinonyl, 2-pyrimidinonyl, 2-pyrollidinonyl, quinolinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, and thienyl.

The term "heteroatom" means O, S or N, selected on an independent basis.

The term “heteroaryl” refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one or two additional carbon atoms is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms, said heteroaryl group being optionally substituted as described herein. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, thienyl and triazolyl. Additional nitrogen atoms may be present together with the first nitrogen and oxygen or sulfur, giving, e.g., thiadiazole.

This invention is also concerned with compositions and methods of treating ocular hypertension or glaucoma by administering to a patient in need thereof one of the compounds of formula I alone or in combination with one or more of the following active ingredients,in combination with a β-adrenergic blocking agent such as timolol, betaxolol, levobetaxolol, carteolol, levobunolol, a parasympathomimetic agent such as epinephrine, iopidine, brimonidine, clonidine, para-aminoclonidine, carbonic anhydrase inhibitor such as dorzolamide, acetazolamide, metazolamide or brinzolamide, an EP4 agonist (such as those disclosed in WO 02/24647, WO 02/42268, EP 1114816, WO 01/46140, PCT Appln. No. CA2004000471, and WO 01/72268), a prostaglandin such as latanoprost, travaprost, unoprostone, rescula, S1033 (compounds set forth in US Patent Nos. 5,889,052; 5,296,504; 5,422,368; and 5,151,444); a hypotensive lipid such as lumigan and the compounds set forth in US Patent No. 5,352,708; a neuroprotectant disclosed in US Patent No. 4,690,931, particularly eliprodil and R-eliprodil as set forth in WO 94/13275, including memantine; an agonist of 5-HT2 receptors as set forth in PCT/US00/31247, particularly 1-(2-aminopropyl)-3-methyl-1H-imdazol-6-ol fumarate and 2-(3-chloro-6-methoxy-indazol-1-yl)-1-methyl-ethylamine or a mixture thereof. An example of a hypotensive lipid (the carboxylic acid group on the α-chain link of the basic prostaglandin structure is replaced with electrochemically neutral substituents) is that in which the carboxylic acid group is replaced with a C_{1-6} alkoxy group such as OCH_3 (PGF_{2a} 1-OCH_3), or a hydroxy group (PGF_{2a} 1-OH).

Preferred potassium channel blockers are calcium activated potassium channel blockers. More preferred potassium channel blockers are high conductance, calcium activated potassium (Maxi-K) channel blockers. Maxi-K channels are a family of ion channels that are prevalent in neuronal, smooth muscle and epithelial tissues and which are gated by membrane potential and intracellular Ca^{2+}.

The present invention is based upon the finding that maxi-K channels, if blocked, inhibit aqueous humor production by inhibiting net solute and H_2O efflux and therefore lower IOP. This finding suggests that maxi-K channel blockers are useful for treating other ophthamological dysfunctions such as macular edema and macular degeneration. It is known that lowering IOP promotes blood flow to the retina and optic nerve. Accordingly, the compounds of this invention are useful for treating macular edema and/or macular degeneration. Use of a compound of formula I in claim 1 for the manufacture of a medicament for the treatment of macular edema and/or macular degeneration

It is believed that maxi-K channel blockers which lower IOP are useful for providing a neuroprotective effect. They are also believed to be effective for increasing retinal and optic nerve head blood velocity and increasing retinal and optic nerve oxygen by lowering IOP, which when coupled together benefits optic nerve health. As a result, this invention further relates to a method for increasing retinal and optic nerve head blood velocity, increasing retinal and optic nerve oxygen tension as well as providing a neuroprotective effect or a combination thereof. Use of a compound of formula I in claim 1 for the manufacture of a medicament for increasing retinal and optic nerve head blood velocity, retinal and optic nerve oxygen tension and providing a neuroprotective effect.

A number of marketed drugs function as potassium channel antagonists. The most important of these include the compounds Glyburide, Glipizide and Tolbutamide. These potassium channel antagonists are useful as antidiabetic agents. The compounds of this invention may be combined with one or more of these compounds to treat diabetes. Use of a compound of formula I in claim 1 for the manufacture of a medicament for the treatment of diabetes.

Potassium channel antagonists are also utilized as Class 3 antiarrhythmic agents and to treat acute infarctions in humans. A number of naturally occuring toxins are known to block potassium channels including Apamin, Iberiotoxin, Charybdotoxin, Noxiustoxin, Kaliotoxin, Dendrotoxin(s), mast cell degranuating (MCD) peptide, and β-Bungarotoxin (β-BTX). The compounds of this invention may be combined with one or more of these compounds to treat arrhythmias. Use of a compound of formula I in claim 1 in combination with these compounds for the manufacture of a medicament for the treatment of arrhythmias

Depression is related to a decrease in neurotransmitter release. Current treatments of depression include blockers of neurotransmitter uptake, and inhibitors of enzymes involved in neurotransmitter degradation which act to prolong the lifetime of neurotransmitters.

Alzheimer's disease is also characterized by a diminished neurotransmitter release. Three classes of drugs are being investigated for the treatment of Alzheimer's disease cholinergic potentiators such as the anticholinesterase drugs (e.g., physostigmine (eserine), and Tacrine (tetrahydroaminocridine)); nootropics that affect neuron metabolism with little effect elsewhere (e.g., Piracetam, Oxiracetam; and those drugs that affect brain vasculature such as a mixture of ergoloid mesylates amd calcium channel blocking drugs including Nimodipine. Selegiline, a monoamine oxidase B inhibitor which increases brain dopamine and norepinephrine has reportedly caused mild improvement in some Alzheimer's patients. Aluminum chelating agents have been of interest to those who believe Alzheimer's disease is due to aluminum toxicity. Drugs that affect behavior, including neuroleptics, and anxiolytics have been employed. Anxiolytics, which are mild tranquilizers, are less effective than neuroleptics The present invention is related to novel compounds which are useful as potassium channel antagonists. Use of a compound of formula I in claim 1 for the manufacture of a medicament for the treatment of depression and Alzheimer's disease.

The compounds of this invention may be combined with anticholinesterase drugs such as physostigmine (eserine) and Tacrine (tetrahydroaminocridine), nootropics such as Piracetam, Oxiracetam, ergoloid mesylates, selective calcium channel blockers such as Nimodipine, or monoamine oxidase B inhibitors such as Selegiline, in the treatment of Alzheimer's disease. The compounds of this invention may also be combined with Apamin, Iberiotoxin, Charybdotoxin, Noxiustoxin, Kaliotoxin, Dendrotoxin(s), mast cell degranuating (MCD) peptide, β-Bungarotoxin (β-BTX) or a combination thereof in treating arrythmias. The compounds of this invention may further be combined with Glyburide, Glipizide, Tolbutamide or a combination thereof to treat diabetes.

The herein examples illustrate but do not limit the claimed invention. Each of the claimed compounds are potassium channel antagonists and are thus useful in the described neurological disorders in which it is desirable to maintain the cell in a depolarized state to achieve maximal neurotransmitter release. The compounds produced in the present invention are readily combined with suitable and known pharmaceutically acceptable excipients to produce compositions which may be administered to mammals, including humans, to achieve effective potassium channel blockage.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable

organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N^1-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

The maxi-K channel blockers used can be administered in a therapeutically effective amount intravaneously, subcutaneously, topically, transdermally, parenterally or any other method known to those skilled in the art.

Ophthalmic pharmaceutical compositions are preferably adapted for topical administration to the eye in the form of solutions, suspensions, ointments, creams or as a solid insert. Ophthalmic formulations of this compound may contain from 0.01 ppm to 1% and especially 0.1 ppm to 1% of medicament. Higher dosages as, for example, about 10% or lower dosages can be employed provided the dose is effective in reducing intraocular pressure, treating glaucoma, increasing blood flow velocity or oxygen tension. For a single dose, from between 0. 1 ng to 5000 ug, preferably 1 ng to 500 ug, and especially 10 ng to 100 ug of the compound can be applied to the human eye.

The pharmaceutical preparation which contains the compound may be conveniently admixed with a non-toxic pharmaceutical organic carrier, or with a non-toxic pharmaceutical inorganic carrier. Typical of pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethyl-cellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetracetic acid, and the like. Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate vehicles and the like. The pharmaceutical preparation may also be in the form of a microparticle formulation. The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. The polymer used to form the insert may be any water soluble non-toxic polymer, for example, cellulose derivatives such as methylcellulose, sodium carboxymethyl cellulose, (hydroxyloweralkyl cellulose), hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose; acrylates such as polyacrylic acid salts, ethylacrylates, polyactylamides; natural products such as gelatin, alginates, pectins, tragacanth, karaya, chondrus, agar, acacia; the starch derivatives such as starch acetate, hydroxymethyl starch ethers, hydroxypropyl starch, as well as other synthetic derivatives such as polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl methyl ether, polyethylene oxide, neutralized carbopol and xanthan gum, gellan gum, and mixtures of said polymer.

Suitable subjects for the administration of the formulation of the present invention include primates, man and other animals, particularly man and domesticated animals such as cats and dogs.

The pharmaceutical preparation may contain non-toxic auxiliary substances such as antibacterial components which are non-injurious in use, for example, thimerosal, benzalkonium chloride, methyl and propyl paraben, benzyldodecinium bromide, benzyl alcohol, or phenylethanol; buffering ingredients such as sodium chloride, sodium borate, sodium acetate, sodium citrate, or

gluconate buffers; and other conventional ingredients such as sorbitan monolaurate, triethanolamine, polyoxyethylene sorbitan monopalmitylate, ethylenediamine tetraacetic acid, and the like.

The ophthalmic solution or suspension may be administered as often as necessary to maintain an acceptable IOP level in the eye. It is contemplated that administration to the mamalian eye will be about once or twice daily.

For topical ocular administration the novel formulations of this invention may take the form of solutions, gels, ointments, suspensions or solid inserts, formulated so that a unit dosage comprises a therapeutically effective amount of the active component or some multiple thereof in the case of a combination therapy.

The following examples, given by way of illustration, are demonstrative of the present invention.

Definitions of the terms used in the examples are as follows:

SM - Starting material,

DMSO – dimethyl sulfoxide,

TLC – thin layer chromatography,

SGC – silica gel chromatography,

h = hr = hour,

THF – tetrahydrofuran,

DMF – dimethylformamide,

LDA- lithium diisopropylamide,

HOBt – 1-hydroxybenzotriazole hydrate

EDC – 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

NMR-nuclear magnetic resonance,

TFA-trifluoroacetic acid,

DIEA-*N,N*-diisopropylethylamine

min – minute,

LC/MS – liquid chromatography/mass spectrometry,

HPLC – high performance liquid chromatography,

equiv = eq = equivalent,

General Experimental Conditions: NMR spectra were recorded at room temperature on Varian Instruments referenced to residual solvent peak. LC-MS were measured on an Aglient HPLC and Micromass ZQ detector with electrospray ionization using a 2.0x50 mm X-Terra C18 column and 10~98% MeCN gradient over 3.75 minutes followed by 98% MeCN for 1 minute. The aqueous and MeCN eluents contained 0.06 and 0.05% (v/v) trifluoroacetic acid, respectively. Mass peaks are listed in

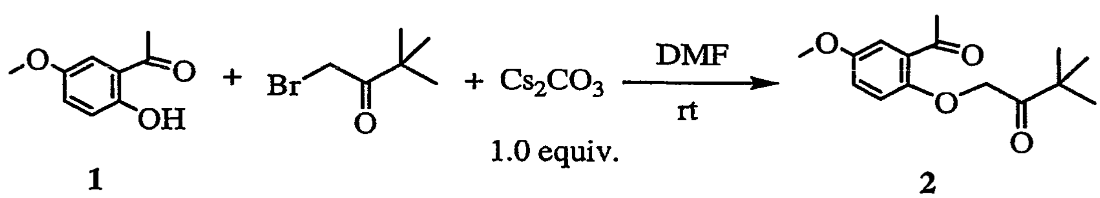
decreasing order of relative abundance. Preparative HPLC separations were done using a C18 column such as YMC 20x150 mm 5 μ ProC18 column or a 9.4x250 mm SB-C18 Zorbax column.

The compounds of this invention can be made, with modification where appropriate, in accordance with Schemes 1-8.

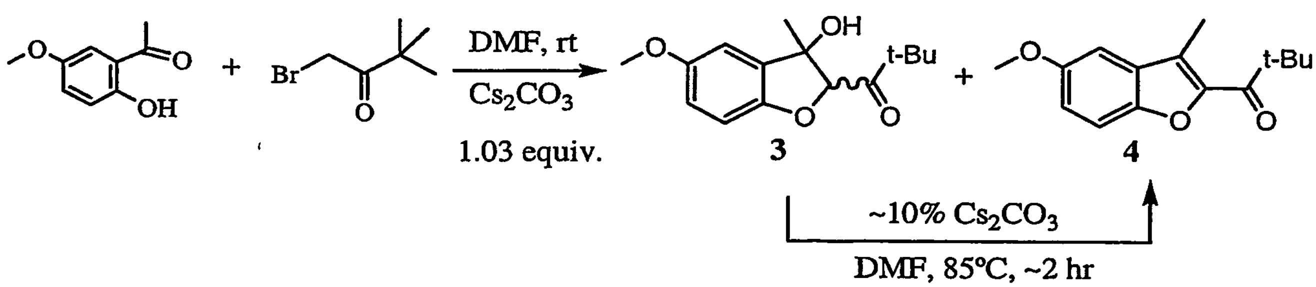
Scheme 1 illustrates a method for preparing one of two common intermediates, benzofuran 4. When the commercially available hydroxyacetophenone 1 was treated with stoichiometric amounts of 1-bromopinacolone and cesium carbonate at room temperature, analysis indicated that the only product was the ether 2 (Method A). When a slight excess of cesium carbonate was employed in the reaction, the product was a mixture of two diastereomers of 3 plus benzofuran 4 (Method B). The intermediate 3 can be converted to 4 in high yields with catalytic amount of cesium carbonate at slightly elevated temperature. This two-step conversion of 1 to 4 can be simplified by conducting the reaction at elevated temperature with a slight excess of cesium carbonate (Method C).

SCHEME 1

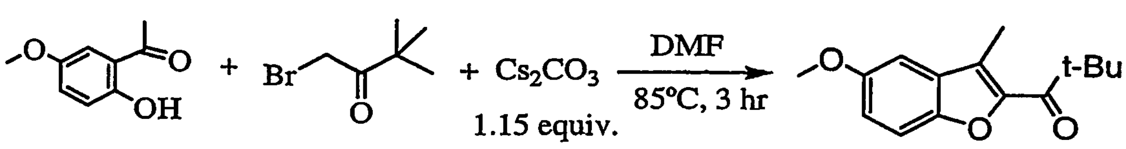
Method A



Method B

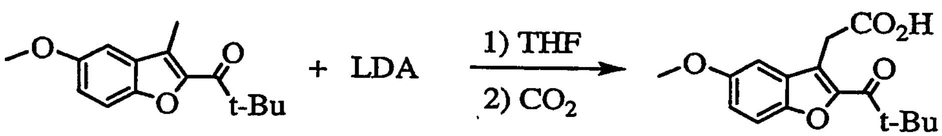


Method C



Scheme 2 illustrates the preparation of a second common intermediate, acid 5. The benzofuran 4 can be carboxylated by treatment with a strong base such as LDA followed by carbon dioxide to give acid 5.

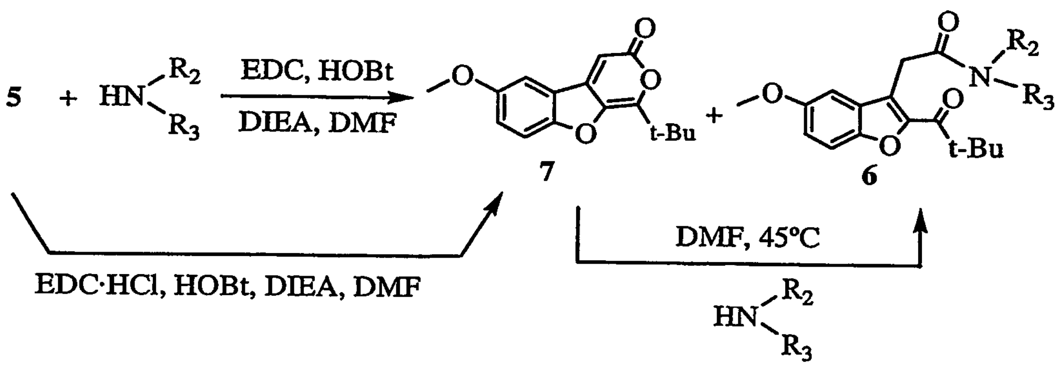
SCHEME 2



5

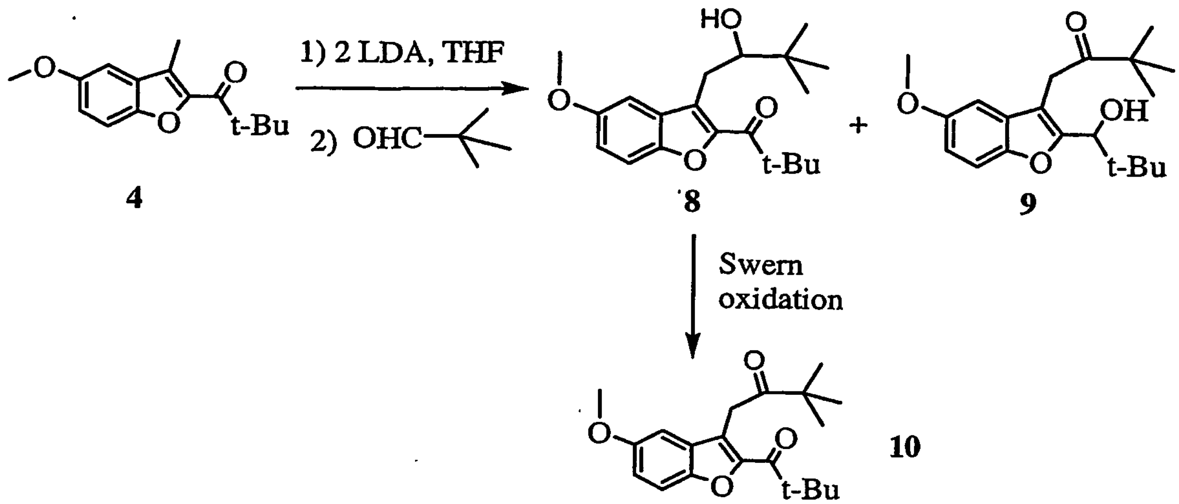
Some compounds of the present invention can be prepared as illustrated in Scheme 3. Many coupling conditions could give amides 6 as the final product. It is usually accompanied by side-product 7. Heating the side-product with amine can give the desired amide also. This side-product can be produced by omitting the dialkyl amine during the coupling reaction. Therefore, the sequence 5-7-6 is an alternative route for the preparation of the compounds of this invention.

SCHEME 3

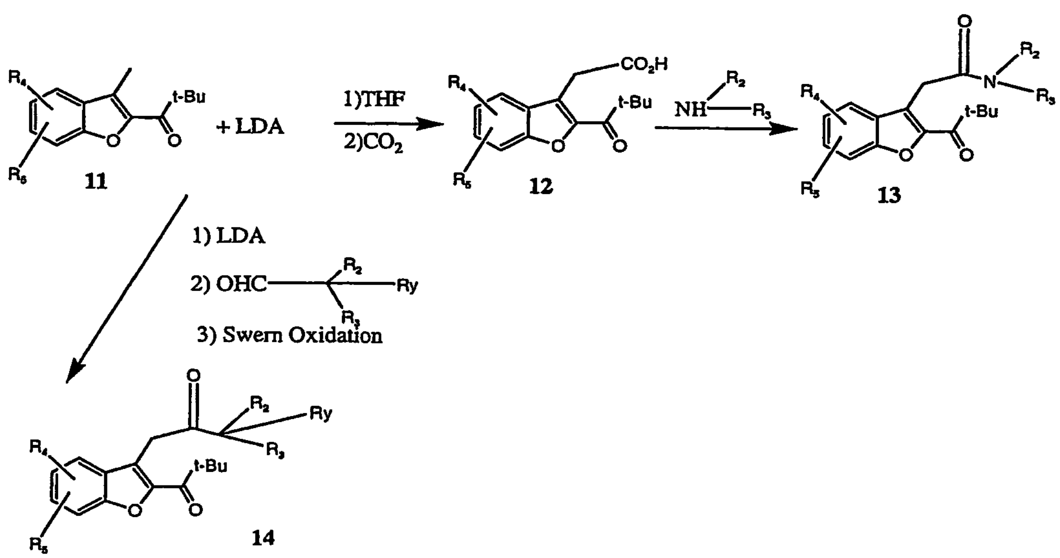


The preparation of another type of compounds of this invention is illustrated in Scheme 4. Quenching the homo-enolate from 4 with trimethyl acetaldehyde gave a mixture of two hydroxyketones 8 and 9. Their oxidation affords diketone 10 as illustrated by the conversion of 8 to 10.

SCHEME 4

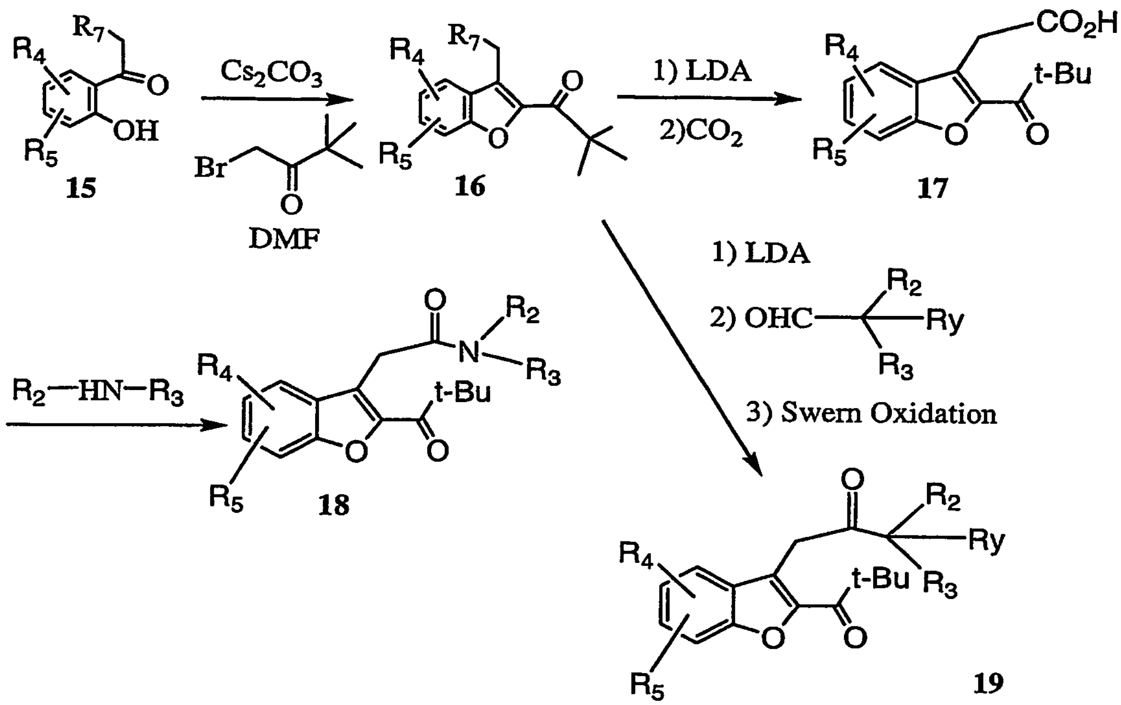


SCHEME 5

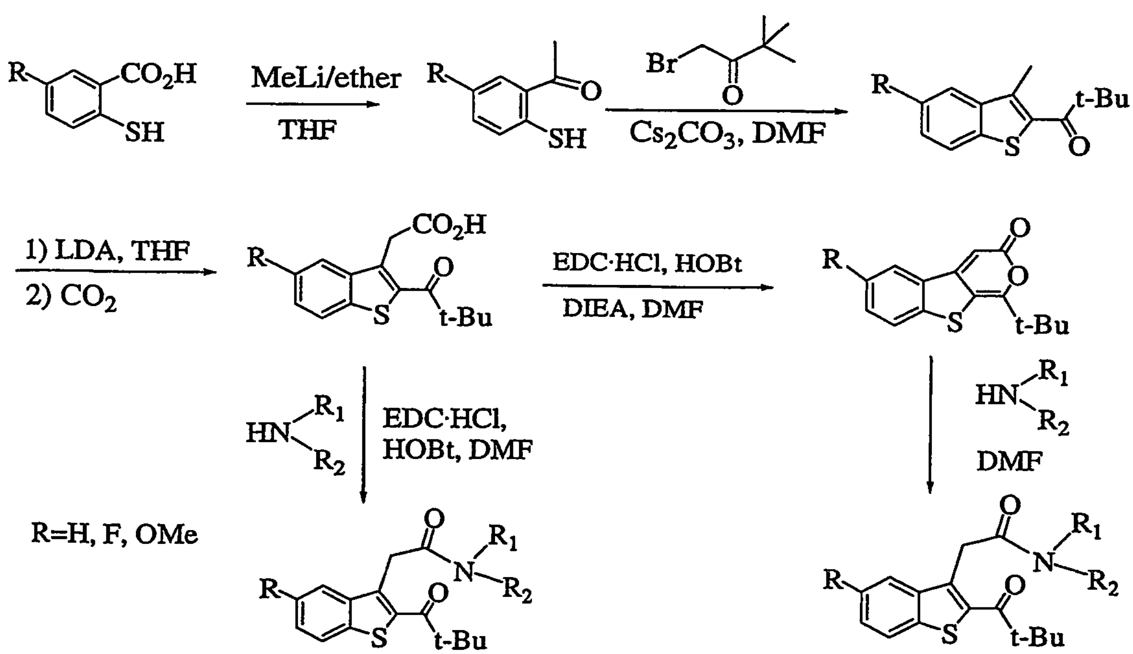


Similarly, substituted analogues such as **11** can be transformed to **13** and **14** using analogous methods. Higher homologues of **1** could be reacted in the same fashion to give desired products **18** and **19** when R7 is not hydrogen (Scheme 6).

SCHEME 6

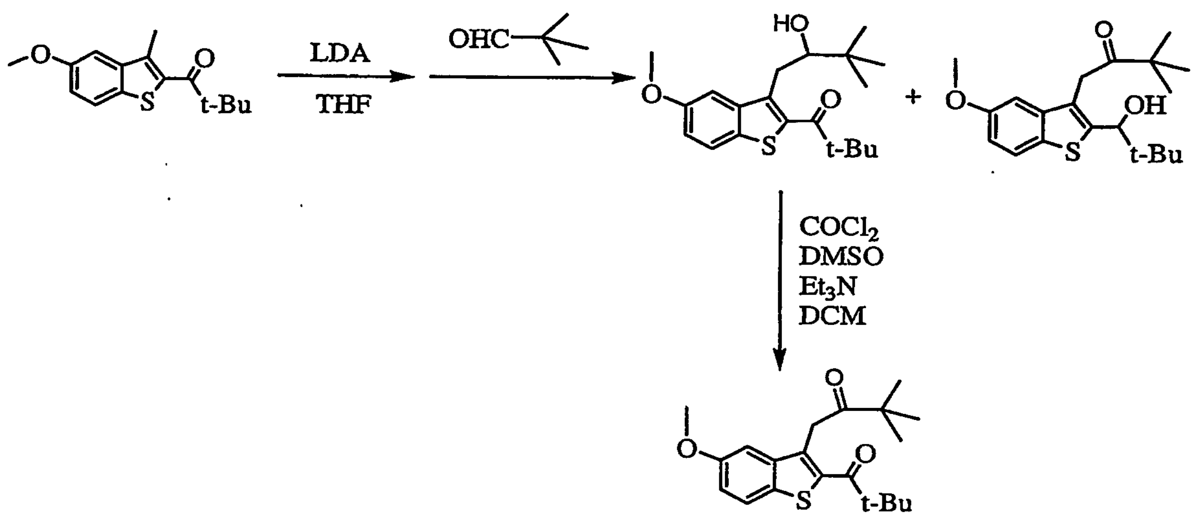


SCHEME 7



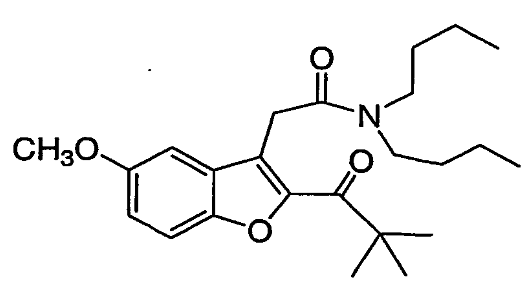
Scheme 7 shows the preparation of amides in the benzothiophene class. The starting 2-mercaptobenzoic acid is either commercially available or prepared based a literature method (C. F. H. Allen and D. D. MacKay *Org. Syn.* Coll Vol II, 580). Treatment of 2-mercaptobenzoic acid with excess methyl lithium provided the methyl ketone (Topolshi, *J. Org. Chem.* 1995, 60, 5585). This was cyclized with α-bromoketone to give benzothiophene in one step using a new procedure. Carboxylation gives the acetic acid derivative and the subsequence conversion to amides are uneventful.

SCHEME 8



Scheme 8 illustrates the synthesis of ketones in the benzothiophene class. A homoaldol reaction between the 3-methyl benzothiophene from Scheme 7 and an aldehyde provided the alcohol precursor to the ketone and an isomeric alcohol. The alcohol intermediate was oxidized to give the ketone using the Swern oxidation.

EXAMPLE 1



N,N-Bibutyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetamide

Step A: 1-(5-Methoxy-3-methyl-1-benzofuran-2-yl)-2,2-dimethylpropan-1-one

DMF (4 mL) was added to a mixture of 166 mg 1-(2-hydroxy-5-methoxyphenyl)ethanone and 370 mg cesium carbonate followed by 188 mg 1-bromopinacolone. After heating this mixture in an 85 °C oil bath for 3 hours, it was poured into cold water and extracted with ether. The combined ether extract was washed with water, 1.5 N NaOH, water, and saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude product. It was purified on silica gel (9:1 hexanes and EtOAc) to give the title compound as a colorless solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (d, J = 9.0 Hz, 1H), 7.11 (dd, J = 2.5 & 9.0 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 3.90 (s, 3H), 2.59 (s, 3H), 1.43 (s, 9H).

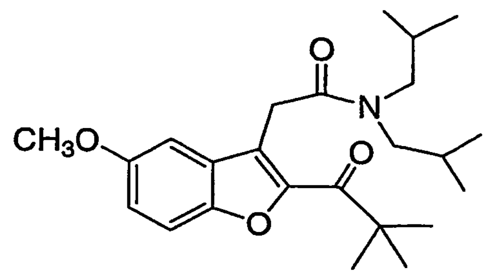
Step B: [2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid

To a solution of 1.23 g 1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-2,2-dimethylpropan-1-one prepared as described in Step A above in 50 mL anhydrous THF at –78 °C was added 5.0 mL 2.0 M LDA in a mixture of heptane, THF, and ethylbenzene. After stirring for 15 minutes, carbon dioxide gas was bubbled into the reaction mixture for 5 minutes. The cooling bath was removed and the reaction mixture was allowed to warm up to room temperature. It was concentrated under reduced pressure to remove solvents. The residue was diluted with ether and extracted with 0.1 M NaOH (3x). The combine aqueous extract was washed with ether, acidified with concentrated HCl to pH ~1, and extracted with ether. The combined ether extract was washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated to give title compound as colorless solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 (d, 9.0 Hz, 1H), 7.18 (dd, 2.5 & 9.2 Hz, 1H), 7.12 (d, 2.5 Hz, 1H), 4.05 (s, 2H), 3.91 (s, 3H), 1.46 (s, 9H). LC-MS: 3.54 min. (m/Z = 245.1, 273.1, 291).

Step C: *N,N*-Bibutyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetamide

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B above and 18.5 mg HOBt in 1 mL dry DMF. Add 14.9 μL di-n-butylamine followed by 23.0 mg EDC and 35 μL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 65-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.46 min. (m/Z = 318.2, 402.2, 424.2).

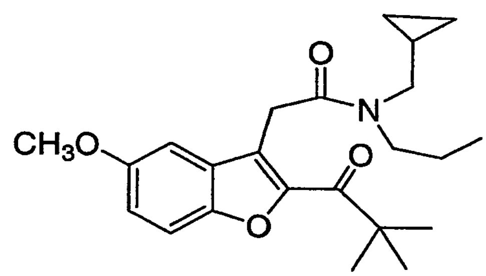
EXAMPLE 2



2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*,*N*-diisobutylacetamide

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 15.4 μL di-i-butylamine followed by 23.0 mg EDC and 35 μL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 65-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.42 min. (m/Z = 318.2, 402.2, 424.2).

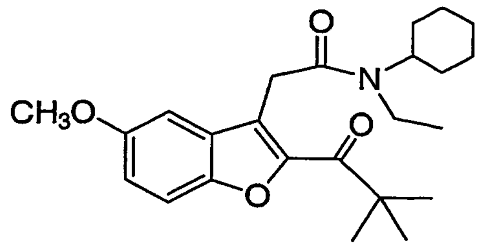
EXAMPLE 3



N-(Cyclopropylmethyl)-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-propylacetamide

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 12.6 μL N-propylcyclopropanemethylamine followed by 23.0 mg EDC and 35 μL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 60-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.17 min. (m/Z = 386.2, 302.1, 408.1).

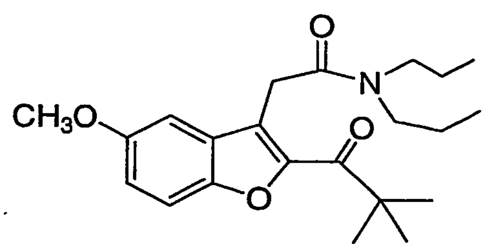
EXAMPLE 4



N-Cyclohexyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-ethylacetamide

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 13.2 μL N-ethylcyclohexylamine followed by 23.0 mg EDC and 35 μL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 65-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.34 min. (m/Z = 400.2, 422.1, 316.1).

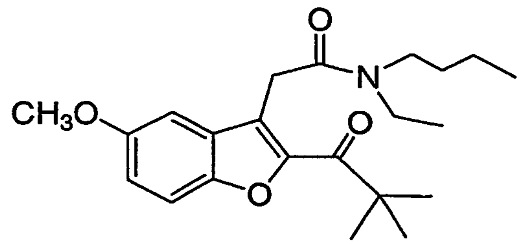
EXAMPLE 5



2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*,*N*-dipropylacetamide

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 12.1 μL dipropylamine followed by 23.0 mg EDC and 35 μL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 60-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.16 min. (m/Z = 290.1, 374.2, 396.1).

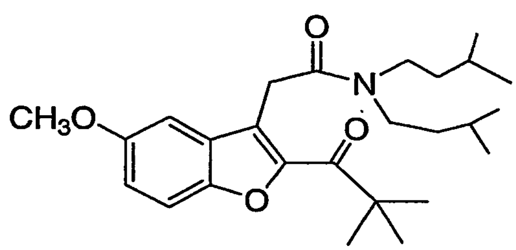
EXAMPLE 6



N-Butyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-ethylacetamide

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 12.0 μL N-ethylbutylamine followed by 23.0 mg EDC and 35 μL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 60-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.15 min. (m/Z = 290.1, 374.2, 396.1).

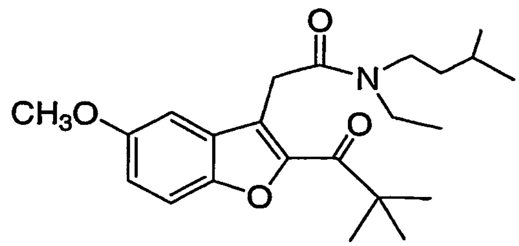
EXAMPLE 7



2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*,*N*-bis(3-methylbutyl)acetamide

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 18.0 μL di-iso-amylamine followed by 23.0 mg EDC and 35 μL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 70-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.67 min. (m/Z = 430.4, 346.2, 452.2).

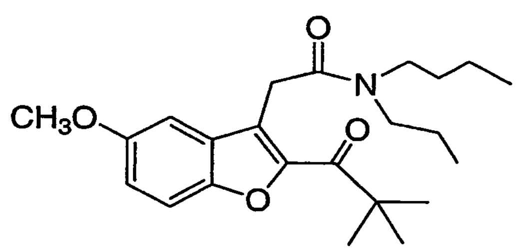
EXAMPLE 8



2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-ethyl-*N*-(3-methylbutyl)acetamide

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 10.1 mg N-ethyl-iso-amylamine followed by 23.0 mg EDC and 35 μL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 65-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.29 min. (m/Z = 304.2, 388.2, 410.2).

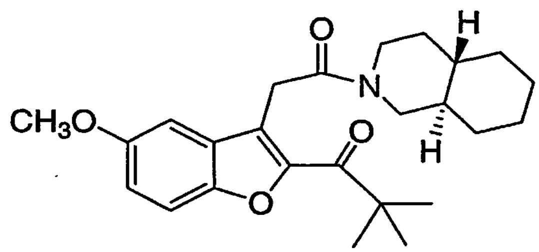
EXAMPLE 9



N-Butyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-propylacetamide

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 13.6 µL N-propylbutylamine followed by 23.0 mg EDC and 35 µL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 65-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.31 min. (m/Z = 304.2, 388.2, 410.2).

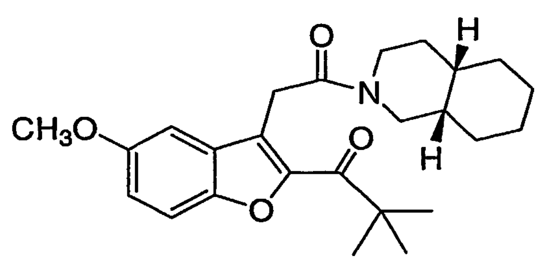
EXAMPLE 10



1-{5-Methoxy-3-[2-(trans-octahydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]-1-benzofuran-2-yl}-2,2-dimethylpropan-1-one

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 12.3 mg trans-decahydroisoquinoline followed by 23.0 mg EDC and 35 µL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 65-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.34 min. (m/Z = 412.3, 328.2, 434.2).

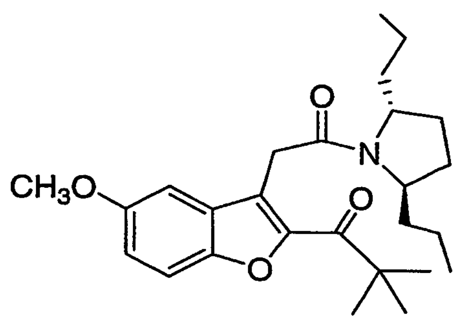
EXAMPLE 11



1-{5-Methoxy-3-[2-(cis-octahydroisoquinolin-2(1*H*)-yl)-2-oxoethyl]-1-benzofuran-2-yl}-2,2-dimethylpropan-1-one

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 12.3 mg cis-decahydroisoquinoline followed by 23.0 mg EDC and 35 μL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 65-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.41 min. (m/Z = 412.3, 328.2, 434.2).

EXAMPLE 12



1-(3-{2-[Trans-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-5-methoxy-1-benzofuran-2-yl)-2,2-dimethylpropan-1-one

Step A: *N,N'*-Dimethoxy-*N,N'*-dimethylsuccinamide

Dissolve 136.2 g of succinyl dichloride and 180.0 g *N,O*-dimethylhydroxylamine hydrochloride in 1.2 L dichloromethane and cool it in an ice bath. Add 305.9 g pyridine from an addition funnel with stir over 1.5 hours. Let the reaction mixture warm up to room temperature over night. Pour the reaction mixture into ice and water and separate the layers. Wash the organic layer with cold 2 N HCl (2x), water, 5% $NaHCO_3$ (2x), and saturated brine. Dry over anhydrous Na_2SO_4 and evaporate to give crude product. It was washed with 3:1 hexanes and dichloromethane and dried to give the title compound as a light tan solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.70 (s, 6H), 3.15 (s, 6H), 2.74 (s, 4H).

Step B: Decane-4,7-dione

Cool a suspension of 20.42 g *N,N'*-dimethoxy-*N,N'*-dimethylsuccinamide from the Step A above in 1 L anhydrous ether in an ice bath under nitrogen. Add 300 mL of 2 M propylmagnesium chloride in ether over 15 minutes with mechanical stir. Continue to stir the reaction mixture in the cooling bath for 2.25 hours. Quench the reaction by adding 30 mL ethanol in 50 mL ether over 30 minutes. Pour the resulting suspension into 1 L ice and water containing 75 mL concentrated HCl. Separate the layers, wash the organic layer with dilute HCl, 5% $NaHCO_3$ and saturated brine. Dry over anhydrous Na_2SO_4. Evaporate the clear yellowish solution to give the title compound as yellow solid. ^{1}H

NMR ($CDCl_3$, 500 MHz) δ: 2.69 (s, 4H), 2.46 (t, J = 7.4 Hz, 4H), 1.60~1.67 (m, 4H), 0.935 (t, J = 7.5 Hz, 6H).

Step C: Cis- and trans-1-benzyl-2,5-dipropylpyrrolidine

Dissolve 11.92 g decane-4,7-dione from the Step B above in 4.62 g acetic acid and 100 mL methanol. Add 1.16 g potassium hydroxide pellets. Stir to dissolve the potassium hydroxide. Cool the reaction mixture in an ice acetone bath at –15 ° C. Add 7.50 g benzylamine followed immediately with 5.4 g sodium cyanoborohydride in several portions. Let the reaction mixture warm up to room temperature over two days. Add 45 mL 4 N HCl drop-wise and stir for 30 minutes. Evaporate the reaction mixture under reduced pressure to remove most of the solvents. Dilute the residue with water, filter off some white solid, and extract the aqueous layer with ether. This ether solution contained 2,5-dipropylpyrrole. Cool the aqueous layer with an ice bath and add solid sodium hydroxide in small portions with stir until pH ~13. Dissolve the white solid above in this mixture. Extract with ether several times. Wash the combined ether solution with saturated brine, dry over anhydrous Na_2SO_4 and evaporate to give the crude 1-benzyl-2,5-dipropylpyrrolidine. The cis and trans isomers were separated on silica gel (5~10% EtOAc in hexanes with 1% Et_3N). The fast eluting isomer was trans-1-benzyl-2,5-dipropylpyrrolidine. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38 (d, J = 7.6 Hz, 2H), 7.29~7.33 (m, 2H), 7.21~7.24 (m, 1H), 3.83 (d, J = 13.9 Hz, 1H), 3.66 (d, J = 14.0 Hz, 1H), 2.86 (br s, 2H), 1.85~1.94 (m, 2H), 1.45~1.60 (m, 4H), 1.27~1.37 (m, 2H), 1.09~1.20 (m, 4H), 0.875 (t, J = 7.2 Hz, 6H). The slower-eluting isomer was cis-1-benzyl-2,5-dipropylpyrrolidine. ^1H NMR ($CDCl_3$, 500 MHz) δ7.29~7.35 (m, 4H), 7.24~7.26 (m, 1H), 3.77 (s, 2H), 2.53~2.58 (m, 2H), 1.77~1.84 (m, 2H), 1.52~1.58 (m, 2H), 1.27~1.44 (m, 4H), 1.13~1.25 (m, 4H), 0.865 (t, J = 7.2 Hz, 6H).

Step D: Trans-2,5-dipropylpyrrolidine

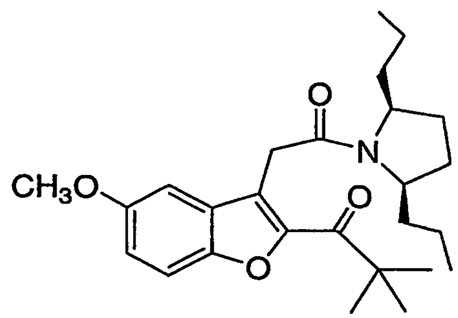
Dissolve 1.56 g trans-1-benzyl-2,5-dipropylpyrrolidine from the Step C above in 100 mL methanol and add 4.01 g ammonium formate and 156 mg $Pd(OH)_2/C$. Let the reaction mixture stir under nitrogen over night. Filter the reaction mixture through Celite to remove the catalyst. Concentrate the filtrate under reduced pressure to give a white solid residue. Suspend it in a small amount of water, add 5 mL 5 N NaOH solution, extract with ether several times, wash the combined ether solution with saturated brine, dry over anhydrous Na_2SO_4, and evaporate to give the title compound as yellow liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ3.11~3.16 (m, 2H), 1.91~1.98 (m, 2H), 1.26~1.50 (m, 10H), 0.93 (t, J = 7.1 Hz, 6H). LC-MS: 1.89 min. (M+H = 156.1).

Step E: 1-(3-{2-[Trans-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-5-methoxy-1-benzofuran-2-yl)-2,2-dimethylpropan-1-one

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 13.7 mg trans-2,5-dipropylpyrrolidine from the Step D above followed by 23.0 mg EDC and 35 μL DIEA. This solution

was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 70-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.58 min. (m/Z = 428.3, 344.2, 450.3).

EXAMPLE 13



1-(3-{2-[Cis-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-5-methoxy-1-benzofuran-2-yl)-2,2-dimethylpropan-1-one

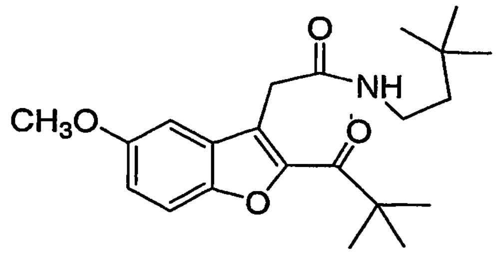
Step A: Cis-2,5-dipropylpyrrolidine

The title compound was prepared in the same manner from cis-1-benzyl-2,5-dipropylpyrrolidine from Step C Example 12 using the procedure in Step D Example 12. ^{1}H NMR ($CDCl_3$, 500 MHz) δ2.94~3.00 (m, 2H), 1.81~1.89 (m, 2H), 1.25~1.54 (m, 10H), 0.94 (t, J = 7.2 Hz, 6H). LC-MS: 1.83 min. (M+H = 156.1).

Step B: 1-(3-{2-[Cis-2,5-dipropylpyrrolidin-1-yl]-2-oxoethyl}-5-methoxy-1-benzofuran-2-yl)-2,2-dimethylpropan-1-one

Dissolve a mixture of 17 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1 and 18.5 mg HOBt in 1 mL dry DMF. Add 13.7 mg cis-2,5-dipropylpyrrolidine from the Step A above followed by 23.0 mg EDC and 35 μL DIEA. This solution was heated at 40 °C for 2 hours. It was purified directly on RP-HPLC using 70-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.59 min. (m/Z = 428.3, 344.2, 450.3).

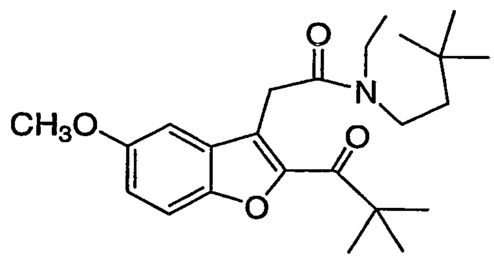
EXAMPLE 14



N-(3,3-Dimethylbutyl)-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetamide

To a mixture of 29 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1, 23 mg HOBt, and 38.3 mg EDC was added 1 mL dry DMF. Add 24.9 mg (3,3-dimethylbutyl)amine hydrochloride followed by 61 μL DIEA. This solution was heated at 45 °C for 2 hours. It was purified directly on RP-HPLC using 60-75% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.08 min. (m/Z = 290.1, 374.2, 396.2).

EXAMPLE 15



N-(3,3-Dimethylbutyl)-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-ethylacetamide

Step A: *N*-Ethyl-3,3-dimethylbutan-1-amine hydrochloride

The title compound was prepared from commercially available ethylamine and 3,3-dimethylbutyraldehye using sodium triacetoxyborohydride (Abdel-Magid, et al. J. Org. Chem. 1996, 61, 3849). ^{1}H NMR (CD_3OD, 500 MHz) δ 3.07 (q, 7.1 Hz, 2H), 2.97~3.02 (m, 2H), 1.57~1.62 (m, 2H), 1.32 (t, 7.2 Hz, 3H), 0.98 (s, 9H).

Step B: 1-*tert*-butyl-6-methoxy-3*H*-pyrano[3,4-*b*][1]benzofuran-3-one

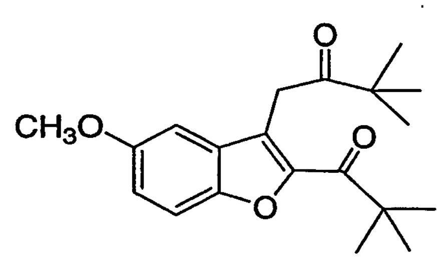
Dissolve 98 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1, 176 μL DIEA, and 114 mg HOBt in 3.5 mL dry DMF. Add 97.1 mg EDC and let the mixture stir at room temperature over night. It was purified directly on RP-HPLC using 50-

70% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound as yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.34 (dd, J = 1.3 & 8.4 Hz, 1H), 7.25~7.29 (m, 2H), 6.54 (s, 1H), 3.92 (s, 3H), 1.52 (s, 9H). LC-MS: 3.55 min. (M+H = 273.1).

Step C: *N*-(3,3-dimethylbutyl)-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-ethylacetamide To a mixture containing 21.8 mg 1-*tert*-butyl-6-methoxy-3*H*-pyrano[3,4-*b*][1]benzofuran-3-one from the Step B above and 21.6 mg *N*-Ethyl-3,3-dimethylbutan-1-amine hydrochloride from the Step A above in 0.75 mL DMF was 26 μL DIEA. The mixture was heated in 45 °C oil bath over night. It was purified directly on RP-HPLC using 65~85% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.38 min. (m/Z = 318.2, 402.3, 424.3). Alternative preparation of *N*-(3,3-dimethylbutyl)-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-ethylacetamide

To a mixture of 7.7 mg [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]acetic acid from the Step B Example 1, 6.1 mg HOBt, and 10.2 mg EDC was added 0.5 mL dry DMF. Add 6.6 *N*-ethyl-3,3-dimethylbutan-1-amine hydrochloride from the Step A above followed by 16 μL DIEA. This solution was heated at 45 °C over night. It was purified directly on RP-HPLC using 65-80% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. LC-MS: 4.38 min. (m/Z = 424.3, 318.2, 402.3).

EXAMPLE 16



1-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-3,3-dimethylbutan-2-one

Step A: 1-[3-(2-Hydroxy-3,3-dimethylbutyl)-5-methoxy-1-benzofuran-2-yl]-2,2-dimethylpropan-1-one

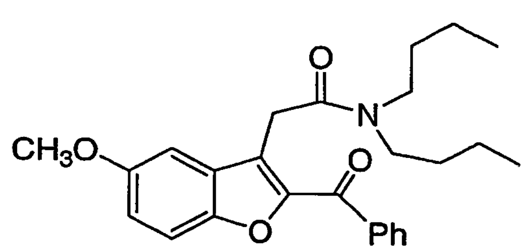
To a solution of 0.23 g 1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-2,2-dimethylpropan-1-one from Step A Example 1 in 10 mL anhydrous THF at –78 °C under nitrogen was added 0.93 mL 2 M LDA in heptane, THF, and ethylbenzene. After 15 minutes, 0.160 g trimethylacetaldehyde was added. Remove the cooling bath and let the reaction mixture warm up to room temperature. After 30 minutes, evaporate the reaction mixture under reduced pressure to remove solvents. Dilute the residue with ether,

wash with 1 M HCl (2x) and saturated brine, dry over anhydrous Na_2SO_4, and evaporate to give a crude product. It was purified on RP-HPLC using 75~100% MeCN in water without TFA to give the title compound as colorless solid after lyophilization. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.44 (d, J = 9.2 Hz, 1H), 7.12 (dd, J = 2.7 & 9.1 Hz, 1H), 7.02 (d, J = 2.5 Hz, 1H), 3.89 (s, 3H), 3.48~3.52 (br m, 1H), 3.40 (br d, J = 7.0 Hz, 1OH), 3.10~3.16 (m, 2H), 1.43 (s, 9H), 1.10 (s, 9H). LC-MS: 4.23 min. (m/Z = 245.2, 315.2, 355.2 = M + Na, 259.1). A faster-eluting isomeric side-product was also isolated during purification: 1-[2-(1-hydroxy-2,2-dimethylpropyl)-5-methoxy-1-benzofuran-3-yl]-3,3-dimethylbutan-2-one. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.34 (d, J = 8.9 Hz, 1H), 6.87 (dd, J = 2.5 & 9.0 Hz, 1H), 6.79 (d, J = 2.5 Hz, 1H), 4.53 (s, 1H), 3.99 (d, J = 17.6 Hz, 1H), 3.92 (d, J = 17.4 Hz, 1H), 3.84 (s, 3H), 1.32 (s, 9H), 1.06 (s, 9H). LC-MS: 3.77 min. (m/Z = 355.2 = M + Na, 315.2). The structures of the isomers were further confirmed by COSY and NOESY spectroscopy.

Step B: 1-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-3,3-dimethylbutan-2-one

Cool 1.5 mL dichloromethane in dry ice bath under nitrogen. Add 38 mg oxalyl chloride followed by 47 mg DMSO. Stir for 30 minutes. Add a solution of 49.9 mg 1-[3-(2-hydroxy-3,3-dimethylbutyl)-5-methoxy-1-benzofuran-2-yl]-2,2-dimethylpropan-1-one from the Step A above in 2.5 mL dichloromethane. After another 25 minutes, 167 μL triethylamine were added. After stirring for additional 25 minutes, the reaction mixture was removed from the cooling bath and allowed to warm to room temperature. After 2 hours, solvents were removed under reduced pressure and the residue was purified directly on RP-HPLC using 70-100% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.43 (d, J = 8.9 Hz, 1H), 7.10 (dd, J = 2.5 & 8.9 Hz, 1H), 6.90 (d, J = 2.6 Hz, 1H), 4.39 (s, 2H), 3.87 (s, 3H), 1.42 (s, 9H), 1.34 (s, 9H). LC-MS: 4.17 min. (m/Z = 247.2, 353.3, 331.4).

EXAMPLE 17



2-(2-Benzoyl-5-methoxy-1-benzofuran-3-yl)-*N*,*N*-dibutylacetamide

Step A: (5-Methoxy-3-methyl-1-benzofuran-2-yl)(phenyl)methanone

The title compound was prepared from 1-(2-hydroxy-5-methoxyphenyl)ethanone, 2-bromoacetophenone, and cesium carbonate using the procedure described in Step A, Example 1. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03~8.07 (m, 2H), 7.55~7.59 (m, 1H), 7.47~7.51 (m, 2H), 7.40 (d, J = 9.0 Hz, 1H), 7.08 (dd, J = 2.6 & 9.0 Hz, 1H), 7.03 (d, J = 2.5 Hz, 1H), 3.86 (s, 3H), 2.59 (s, 3H). LC-MS: 3.83 min. (M+H = 267.2)

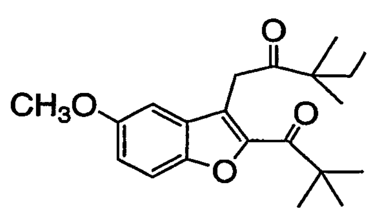
Step B: (2-Benzoyl-5-methoxy-1-benzofuran-3-yl)acetic acid

The title compound was prepared from (5-methoxy-3-methyl-1-benzofuran-2-yl)(phenyl)methanone from the Step A above using procedure in Step B Example 1. The crude acidic fraction was further purified on RP-HPLC using 40~75% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22~8.24 (m, 2H), 7.69~7.73 (m, 1H), 7.58~7.62 (m, 2H), 7.51 (d, J = 8.9 Hz, 1H), 7.21 (dd, J = 2.5 & 8.9 Hz, 1H), 7.18 (d, J = 2.3 Hz, 1H), 4.17 (s, 2H), 3.93 (s, 3H). LC-MS: 3.26 min. (m/Z = 265.2, 293.2).

Step C: 2-(2-Benzoyl-5-methoxy-1-benzofuran-3-yl)-*N*,*N*-dibutylacetamide

To a mixture of 10.6 mg (2-benzoyl-5-methoxy-1-benzofuran-3-yl)acetic acid from the Step B above, 7.8 mg HOBt and 13.1 mg EDC were added 6.6 mg dibutylamine and 0.5 mL DMF followed by 21 μL DIEA. After stirring at room temperature over night, it was heated in a 55 °C oil bath for 8 hours. It was purified directly on RP-HPLC using 60-95% MeCN gradient. The fractions containing pure product were pooled and lyophilized to give the title compound. ^{1}H NMR ($CDCl_3$, 500 MHz) δ8.10~8.13 (m, 2H), 7.62~7.66 (m, 1H), 7.53~7.57 (m, 2H), 7.45 (d, J = 8.9 Hz, 1H), 7.275 (d, J = 2.7 Hz, 1H), 7.14 (dd, J = 2.7 & 9.1 Hz, 1H), 4.39 (s, 2H), 3.89 (s, 3H), 3.43~3.47 (m, 2H), 3.37~3.40 (m, 2H), 1.51~1.61 (m, 4H), 1.26~1.38 (m, 4H), 0.94 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H). LC-MS: 4.24 min. (m/Z = 422.3, 444.3).

EXAMPLE 18



1-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-3,3-dimethylpentan-2-one

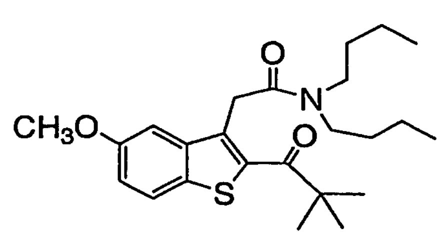
Step A: 1-[3-(2-Hydroxy-3,3-dimethylpentyl)-5-methoxy-1-benzofuran-2-yl]-2,2-dimethylpropan-1-one

To a solution of 0.493 g 1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-2,2-dimethylpropan-1-one from Step A Example 1 in 20 mL anhydrous THF at –78 °C under nitrogen was added 2.0 mL 2 M LDA in heptane, THF, and ethylbenzene. After 50 minutes, 0.40 g 2,2-dimethylbutanal was added. Remove the cooling bath and let the reaction mixture warm up to room temperature. After 70 minutes, the reaction was quenched by adding 2 mL saturated ammonium chloride and the reaction mixture was evaporated under reduced pressure to remove solvents. Dilute the residue with ether, wash with 1 M HCl (2x) and saturated brine, dry over anhydrous Na_2SO_4, and evaporate to give a crude product. It was purified on RP-HPLC using 65~100% MeCN in water without TFA to give the title compound as colorless solid after lyophilization. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.44 (d, 9.1 Hz, 1H), 7.20 (d, 2.0 Hz, 1H), 7.10 (dd, 2.5 & 9.1 Hz, 1H), 3.86 (s, 3H), 3.58 (dd, 1.6 & 10.6 Hz, 1H), 3.29~3.34 (m, 1H), 2.90~2.95 (m, 1H), 1.51~1.59 (m, 1H), 1.39~1.46 (m, 1H), 1.40 (s, 9H), 1.02 (s, 3H), 1.01 (s, 3H), 0.92 (t, 7.6 Hz, 3H). LC-MS: 4.47 min. (m/Z = 329.3, 369.2, 347). A faster-eluting isomeric side-product was also isolated during purification and was identified as 1-[2-(1-hydroxy-2,2-dimethylpropyl)-5-methoxy-1-benzofuran-3-yl]-3,3-dimethylpentan-2-one. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.30 (d, 9.0 Hz, 1H), 6.84 (dd, 2.5 & 8.9 Hz, 1H), 6.75 (d, 2.5 Hz, 1H), 4.44 (s, 1H), 4.07 (AB d, 18.5 Hz, 1H), 4.04 (AB d, 18.5 Hz, 1H), 3.78 (s, 3H), 1.74 (q, 7.6 Hz, 2H), 1.263 (s, 3H), 1.260 (s, 3H), 0.99 (s, 9H), 0.91 (t, 7.4 Hz, 3H). LC-MS: 3.95 min. (m/Z = 369.3= M + Na, 329.3,).

Step B: 1-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-3,3-dimethylpentan-2-one

The title compounds was prepared from 1-[3-(2-hydroxy-3,3-dimethylpentyl)-5-methoxy-1-benzofuran-2-yl]-2,2-dimethylpropan-1-one from Step A above using procedure similar to that in Step B of Example 16. LC-MS: 4.36 min. (m/Z = 261.2, 367.3, 345.3).

EXAMPLE 19



N,N-Dibutyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]acetamide Step A: 1-(2-Mercapto-5-methoxyphenyl)ethanone

The title compound was prepared from crude 2-mercapto-5-methoxybenzoic acid from the method of Allen and MacKay (Org. Syn. Coll Vol II, 580) using the method by Topolski (J. Org. Chem. 1995, 60, 5585). It was used without purification in the next step. LC-MS: 2.91 min. (m/Z = 183).

Step B: 1-(5-Methoxy-3-methyl-1-benzothien-2-yl)-2,2-dimethylpropan-1-one

The title compound was prepared from 1-(2-mercapto-5-methoxyphenyl)ethanone from the Step A above using the method similar to that in Step A Example 1. It was purified by recrystallization from ethyl acetate. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.70 (d, 8.7 Hz, 1H), 7.24 (d, 2.3 Hz, 1H), 7.135 (dd, 2.5 & 8.9 Hz, 1H), 3.93 (s, 3H), 2.56 (s, 3H), 1.41 (s, 9H). LC-MS: 4.17 min. (m/Z = 221.1, 179.0, 263.1).

Step C: [2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]acetic acid The title compound was prepared from 1-(5-methoxy-3-methyl-1-benzothien-2-yl)-2,2-dimethylpropan-1-one from Step B above using the method described in Step B Example 1. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.73 (d, 8.9 Hz, 1H), 7.46 (d, 2.3 Hz, 1H), 7.21 (dd, 2.6 & 9.0 Hz, 1H), 4.01 (s, 2H), 3.95 (s, 3H), 1.47 (s, 9H). LC-MS: 3.48 min. (m/Z = 261.1, 289.1, 329.1, 307).

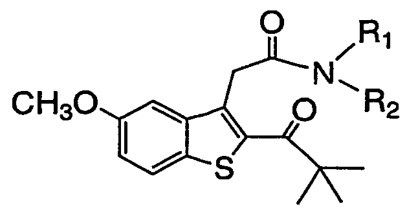
Step D: 1-*tert*-Butyl-6-methoxy-3*H*-[1]benzothieno[2,3-*c*]pyran-3-one

A round bottom flask was charged with 0.460 g [2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]acetic acid from the Step C above, 0.345 g HOBt hydrate, and 0.504 g EDC HCl salt. This mixture was dissolved in 15 mL anhydrous DMF and 0.582 g DIEA was added. The mixture turned bright yellow. After standing at room temperature overnight, the mixture was poured into water and extracted with ether several times. The combined ether extract was washed with water (4x), 5% $NaHCO_3$, and saturated brine, dried over anhydrous Na_2SO_4, and evaporated to give the title compound as a bright yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.49 (d, 8.7 Hz, 1H), 7.35 (d, 2.5 Hz, 1H), 7.20 (dd, 2.5 & 8.9 Hz, 1H), 6.65 (s, 1H), 3.92 (s, 3H), 1.51 (s, 9H). LC-MS: 3.77 min. (m/Z = 289.3).

Step E: *N,N*-Dibutyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]acetamide

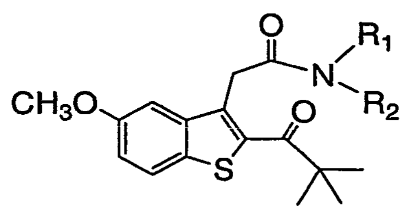
A solution of 21.6 mg of 1-*tert*-butyl-6-methoxy-3*H*-[1]benzothieno[2,3-*c*]pyran-3-one from the Step D above and 29.1 mg di-n-butyl amine in 0.75 mL anhydrous DMF was heated at 70°C for six hours. The reaction mixture was purified on RP-HPLC using 70~100% MeCN gradient with 0.1% TFA. The product fractions were pooled and lyophilized to give the title compound as a white solid. LC-MS: 4.53 min. (m/Z = 418.3, 440.2).

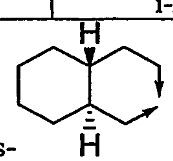
EXAMPLES 20~32

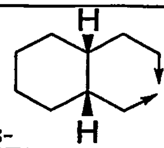
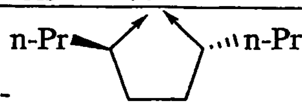
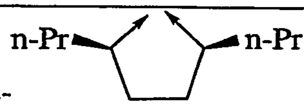


Examples 20~32 in Table 1 were prepared from 1-*tert*-butyl-6-methoxy-3*H*-[1]benzothieno[2,3-*c*]pyran-3-one from the Step D of Example 19 and either three equivalents of an appropriate amine or two equivalents of an appropriate amine plus two equivalents of DIEA under the conditions described in Step E of Example 19. In Example 32, an amine HCl salt was used with the doubled amount of DIEA. The preparation of amines for Examples 30~32 were described in US2003/034959 filed 11/4/03, incorporated herein by reference in its entirety.

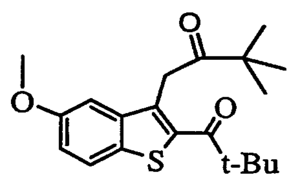
Table 1. Examples 20~32



			LC-MS	
Example	R_1	R_2	t_r, min.	m/Z
20	i-Bu	i-Bu	4.53	418.3, 440.2
21	cyclopropylmethyl	n-Pr	4.25	402.3, 424.2
22	cyclohexyl	Et	4.43	416.3, 438
23	n-Pr	n-Pr	4.24	390.3, 412.2
24	n-Bu	Et	4.24	390.3, 412.2
25	i-Amyl	Et	4.38	404.3, 426
26	n-Bu	n-Pr	4.39	404.3, 426.2
27	i-Amyl	i-Amyl	4.76	446.2, 468.3
28	Trans- 		4.49	428.3, 450.2

29	Cis- 		4.45	428.4, 450.2
30	Trans- 		4.66	444.4, 466.3
31	Cis- 		4.69	444.4, 466.2
32	3,3-Dimethylbutyl	Et	4.48	418.3, 440

EXAMPLE 33



1-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-3,3-dimethylbutan-2-one

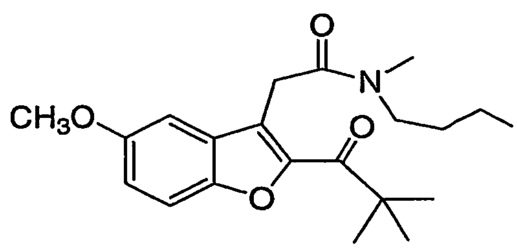
Step A. 1-[3-(2-Hydroxy-3,3-dimethylbutyl)-5-methoxy-1-benzothien-2-yl]-2,2-dimethylpropan-1-one

The title compound was prepared from 1-(5-methoxy-3-methyl-1-benzothien-2-yl)-2,2-dimethylpropan-1-one (Step B, Example 19) using the procedure descried in Step A, Example 18. The products were isolated using RP-HPLC employing a 65~100% MeCN gradient without TFA. The title compound was isolated as the major product as a white solid after lyophilization. ^{1}H NMR (CD_3OD, 500 MHz) δ7.65 (d, 8.7 Hz, 1H), 7.12 (d, 2.3 Hz, 1H), 6.94 (dd, 2.5 & 8.7 Hz, 1H), 4.62 (dd, 2.3 & 2.5 Hz, 1H), 3.87 (s, 3H), 3.00 (dd, 3.0 & 16.0 Hz, 1H), 2.985 (dd, 2.0 & 16.0 Hz, 1H), 1.14 (s, 9H), 1.12 (s, 9H). LC-MS: 4.54 min. (m/Z = 331.2). A faster-eluting isomer was also isolated. It as identified as 1-[2-(1-hydroxy-2,2-dimethylpropyl)-5-methoxy-1-benzothien-3-yl]-3,3-dimethylbutan-2-one. Its ^{1}H NMR (CD_3OD, 500 MHz) δ7.65 (d, 8.7 Hz, 1H), 6.94 (dd, 2.5 & 8.7 Hz, 1H), 6.83 (d, 2.5 Hz, 1H), 4.68 (s, 1H), 4.27 (d, 18.8 Hz, 1H), 4.16 (d, 18.8 Hz, 1H), 3.79 (s, 3H), 1.33 (s, 9H), 1.01 (s, 9H). LC-MS: 3.91 min. (m/Z = 371.1). Unlike the cases in Examples 16 and 18, the two isomers in the current Example appeared to interconvert under ambient temperature and neutral pH spontaneously.

Step B. 1-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzothien-3-yl]-3,3-dimethylbutan-2-one

The title compound was prepared from 1-[3-(2-hydroxy-3,3-dimethylbutyl)-5-methoxy-1-benzothien-2-yl]-2,2-dimethylpropan-1-one from the Step A above using the procedure in Step B, Example 18. It was isolated as a white solid following RP-HPLC purification (70~100% MeCN) and lyophilization. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.72 (d, 8.9 Hz, 1H), 7.13 (dd, 2.4 & 8.8 Hz, 1H), 7.03 (d, 2.6 Hz, 1H), 4.40 (s, 2H), 3.88 (s, 3H), 1.41 (s, 9H), 1.35 (s, 9H). LC-MS: 4.27 min. (m/Z = 369.2, 263.2, 347.3).

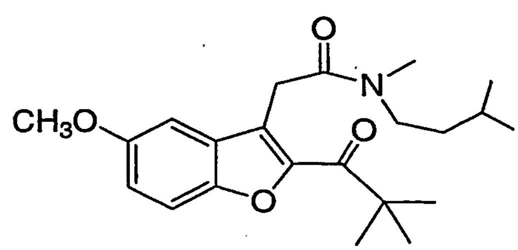
EXAMPLE 34



N-Butyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-methylacetamide

The title compound was prepared from 1-*tert*-butyl-6-methoxy-3*H*-pyrano[3,4-*b*][1]benzofuran-3-one and butyl methyl amine using the procedure from Step C Example 15. LC-MS: 3.97 min. (m/Z = 360.4, 382.3, 276.2, 273.2).

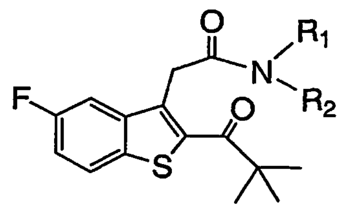
EXAMPLE 35



2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1-benzofuran-3-yl]-*N*-methyl-*N*-(3-methylbutyl)acetamide

The title compound was prepared from 1-*tert*-butyl-6-methoxy-3*H*-pyrano[3,4-*b*][1]benzofuran-3-one and i-amyl methyl amine using the procedure from Step C Example 15. LC-MS: 4.11 min. (m/Z = 374.4, 396.3, 290.3, 273.2).

EXAMPLES 36~49



Step A. 1-(5-Fluoro-2-mercaptophenyl)ethanone

The title compound was prepared from commercially available 5-fluoro-2-mercaptobenzoic acid using the method of Topolski (J. Org. Chem. 1995, 60, 5585). It was purified using SGC with 15~25% EtOAc in hexanes. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.58 (dd, J_{H-H} = 2.8 Hz, J_{H-F} = 9.2 Hz, 1H), 7.31 (dd, J_{H-H} = 8.7 Hz, J_{H-F} = 5.3 Hz, 1H), 7.12 (ddd, J_{H-H} = 8.7 & 2.8 Hz, J_{H-F} = 7.6 Hz, 1H), 4.49 (s, 1 SH), 2.64 (s, 3H).

Step B. 1-(5-Fluoro-3-methyl-1-benzothien-2-yl)-2,2-dimethylpropan-1-one

To a solution of 5.20 g 1-(5-fluoro-2-mercaptophenyl)ethanone in 100 mL anhydrous DMF was added 5.47 g 1-bromopinacolone and 10.95 g cesium carbonate. The resulting mixture was stirred at room temperature overnight and then heated at 70°C for 3 days. After diluting the reaction mixture with ice and water, it was extracted with ether several times. The combined ether extract was washed with 0.05 N NaOH (2x), water (3x), and saturated brine, dried over anhydrous Na_2SO_4, and evaporated to give the crude product. The latter was purified by SGC using 10~15% EtOAc in hexanes to give the title compound as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.77 (dd, J_{H-H} = 8.7 Hz, J_{H-F} = 4.8 Hz, 1H), 7.49 (dd, J_{H-H} = 2.5 Hz, J_{H-F} = 9.6 Hz, 1H), 7.24 (ddd, J_{H-H} = 2.5 & 8.7 Hz, J_{H-F} = 8.7 Hz, 1H), 2.53 (s, 3H), 1.40 (s, 9H). LC-MS: 4.11 min. (m/Z = 209.1, 251.1).

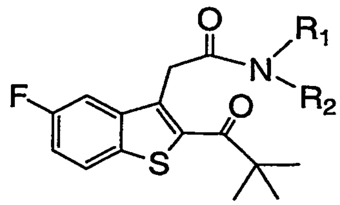
Step C. [2-(2,2-Dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]acetic acid

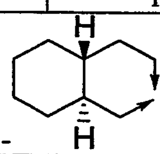
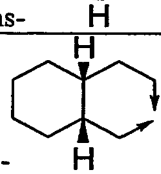
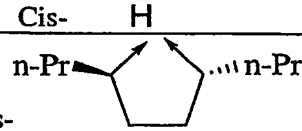
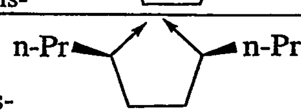
The title compound was prepared from 1-(5-fluoro-3-methyl-1-benzothien-2-yl)-2,2-dimethylpropan-1-one using the procedure described in Step B Example 1. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.82 (dd, J_{H-H} = 8.8 Hz, J_{H-F} = 4.7 Hz, 1H), 7.72 (dd, J_{H-H} = 2.4 Hz, J_{H-F} = 9.3 Hz, 1H), 7.32 (ddd, J_{H-H} = 2.5 & 8.7 Hz, J_{H-F} = 8.7 Hz, 1H), 4.00 (s, 2H), 1.46 (s, 9H). LC-MS: 3.48 min. (m/Z = 249.2, 277.2, 317.2, 295).

Step D. Examples 36~49

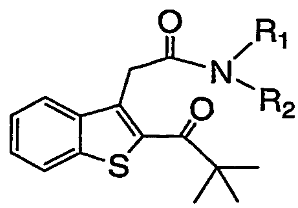
The title compounds were prepared from [2-(2,2-dimethylpropanoyl)-5-fluoro-1-benzothien-3-yl]acetic acid using the same procedure described in Step C Example 1 except the reaction was carried out at 70°C for 8~20 hours.

Table 2. Examples 36~49



			LC-MS	
Example	R_1	R_2	t_r, min.	m/Z
36	n-Bu	n-Bu	4.56	406.3, 428.2
37	i-Bu	i-Bu	4.53	406.3, 428
38	cyclopropylmethyl	n-Pr	4.27	390.3, 412.2
39	cyclohexyl	Et	4.44	404.3, 426
40	n-Pr	n-Pr	4.26	378.3, 400.2
41	n-Bu	Et	4.26	378.3, 400.2
42	i-Amyl	Et	4.40	392.3, 414.2
43	n-Bu	n-Pr	4.41	392.3, 414.2
44	i-Amyl	i-Amyl	4.78	434.3, 456.3
45	Trans- 		4.49	416.3, 438
46	Cis- 		4.46	416.3, 438
47	Trans- 		4.70	432.3, 454.2
48	Cis- 		4.77	432.1, 454.2
49	3,3-Dimethylbutyl	Et	4.50	406.3, 428.2

EXAMPLES 50~63



Step A. 1-(2-Mercaptophenyl)ethanone

The title compound was prepared from commercially available 2-mercaptobenzoic acid using the method of Topolski (J. Org. Chem. 1995, 60, 5585). It was purified using SGC with 15~25% EtOAc in hexanes. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.91 (d, 7.8 Hz, 1H), 7.33~7.35 (m, 2H), 7.21~7.25 (m, 1H), 4.51 (s, 1H), 2.66 (s, 3H). LC-MS: 2.69 min. (m/Z = 59.8, 135.0, 153.0).

Step B. 2,2-Dimethyl-1-(3-methyl-1-benzothien-2-yl)propan-1-one

The title compound was prepared from 1-(2-mercaptophenyl)ethanone and 1-bromopinacolone using the procedure in Step B Examples 36~49. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.82~7.88 (m, 2H), 7.44~7.50 (m, 2H), 2.60 (s, 3H), 1.41 (s, 9H). LC-MS: 4.06 min. (m/Z = 233.4, 191).

Step C. [2-(2,2-Dimethylpropanoyl)-1-benzothien-3-yl]acetic acid

The title compound was prepared from 2,2-dimethyl-1-(3-methyl-1-benzothien-2-yl)propan-1-one using the procedure in Step B Example 1. ^{1}H NMR ($CDCl_3$, 500 MHz) δ8.09 (d, 7.5 Hz, 1H), 7.88 (d, 7.1 Hz, 1H), 7.51~7.58 (m, 2H), 4.06 (s, 2H), 1.48 (s, 9H). LC-MS: 3.36 min. (m/Z = 231.1, 259.1, 299.1, 277).

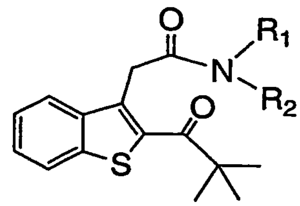
Step D. 1-*tert*-Butyl-3*H*-[1]benzothieno[2,3-*c*]pyran-3-one

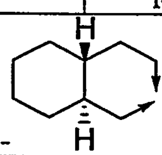
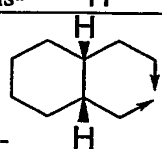
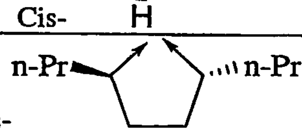
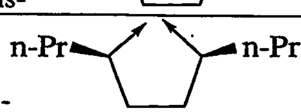
The title compound was prepared from [2-(2,2-dimethylpropanoyl)-1-benzothien-3-yl]acetic acid using the procedure in Step D Examples 20~32. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.93 (d, 8.0 Hz, 1H), 7.62 (d, 8.0 Hz, 1H), 7.56~7.59 (m, 1H), 7.38~7.41 (m, 1H), 6.70 (s, 1H), 1.52 (s, 9H). LC-MS: 3.61 min. (m/Z = 259.2).

Step E. Examples 50~63

Examples 50~63 in Table 3 were prepared from 1-*tert*-butyl-3*H*-[1]benzothieno[2,3-*c*]pyran-3-one and appropriate amine or amine HCl salt using a similar method as the one described in Step E Example 19.

Table 3. Examples 50~63



			LC-MS	
Example	R_1	R_2	t_r, min.	m/Z
50	n-Bu	n-Bu	4.44	388.3, 410.3, 304.2, 259.1
51	i-Bu	i-Bu	4.41	388.3, 410.3, 304.2, 259.2
52	cyclopropylmethyl	n-Pr	4.15	372.3, 394.2, 288.2, 259.2
53	cyclohexyl	Et	4.32	386.3, 408, 259.2, 302.3
54	n-Pr	n-Pr	4.13	360.3, 276.2, 382.3, 259.2
55	n-Bu	Et	4.14	360.3, 276.2, 382.3, 259.2
56	i-Amyl	Et	4.66	416.4, 438, 332.3, 259.2
57	n-Bu	n-Pr	4.28	374.4, 290.3, 396.3, 259.2
58	i-Amyl	i-Amyl	4.30	374.4, 290.3, 396.3, 259.2
59	Trans- 		4.39	398.3, 420.3, 314.3, 259
60	Cis- 		4.35	398.3, 420.3, 314.3, 259
61	Trans- 		4.58	414.4, 436.3, 330.3, 259.2
62	Cis- 		4.61	414.4, 436.3, 330.3, 259.2
63	3,3-Dimethylbutyl	Et	4.38	388.4, 410.3, 304.2, 259.2

FUNCTIONAL ASSAYS

A. Maxi-K Channel

The activity of the compounds can also be quantified by the following assay.

The identification of inhibitors of the Maxi-K channel can be accomplished using Aurora Biosciences technology, and is based on the ability of expressed Maxi-K channels to set cellular resting potential after transient transfection of both α and β subunits of the channel in TsA-201 cells. In the absence of inhibitors, cells display a hyperpolarized membrane potential, negative inside, close to E_K (-80 mV) which is a consequence of the activity of the Maxi-K channel. Blockade of the Maxi-K channel will cause cell depolarization. Changes in membrane potential can be determined with voltage-sensitive fluorescence resonance energy transfer (FRET) dye pairs that use two components, a donor coumarin (CC_2DMPE) and an acceptor oxanol ($DiSBAC_2(3)$). Oxanol is a lipophilic anion and distributes across the membrane according to membrane potential. Under normal conditions, when the inside of the cell is negative with respect to the outside, oxanol is accumulated at the outer leaflet of the membrane and excitation of coumarin will cause FRET to occur. Conditions that lead to membrane depolarization will cause the oxanol to redistribute to the inside of the cell, and, as a consequence, to a decrease in FRET. Thus, the ratio change (donor/acceptor) increases after membrane depolarization.

Transient transfection of the Maxi-K channel in TsA-201 cells can be carried out as previously described (Hanner et al. (1998) J. Biol. Chem. 273, 16289-16296) using FUGENE6™ as the transfection reagent. Twenty four hours after transfection, cells are collected in Ca^{2+}-Mg^{2+}-free Dulbecco's phosphate-buffered saline (D-PBS), subjected to centrifugation, plated onto 96-well poly-d-lysine coated plates at a density of 60,000 cells/well, and incubated overnight. The cells are then washed 1x with D-PBS, and loaded with 100 μl of 4 μM CC_2DMPE-0.02% pluronic-127 in D-PBS. Cells are incubated at room temperature for 30 min in the dark. Afterwards, cells are washed 2x with D-PBS and loaded with 100 μl of 6 μM $DiSBAC_2(3)$ in (mM): 140 NaCl, 0.1 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 20 Hepes-NaOH, pH 7.4, 10 glucose. Test compounds are diluted into this solution, and added at the same time. Cells are incubated at room temperature for 30 min in the dark.

Plates are loaded into a voltage/ion probe reader (VIPR) instrument, and the fluorescence emission of both CC_2DMPE and $DiSBAC_2(3)$ are recorded for 10 sec. At this point, 100 μl of high-potassium solution (mM): 140 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 20 Hepes-KOH, pH 7.4, 10 glucose are added and the fluorescence emission of both dyes recorded for an additional 10 sec. The ratio $CC_2DMPE/DiSBAC_2(3)$, before addition of high-potassium solution equals 1. In the absence of any inhibitor, the ratio after addition of high-potassium solution varies between 1.65-2.0. When the Maxi-K channel has been completely inhibited by either a known standard or test compound, this ratio remains at 1. It is possible, therefore, to titrate the activity of a Maxi-K channel inhibitor by monitoring the concentration-dependent change in the fluorescence ratio.

The compounds of this invention were found to cause concentration-dependent inhibition of the fluorescence ratio with IC_{50}'s in the range of about 1nM to about 20 μM, more preferably from about 10 nM to about 500 nM.

B. Electrophysiological assays of compound effects on high-conductance calcium-activated potassium channels

Human non-pigmented ciliary epithelial cells

The activity of high-conductance calcium-activated potassium (maxi-K) channels in human non-pigmented ciliary epithelial cells was determined using electrophysiological methods. Currents through maxi-K channels were recorded in the inside-out configuration of the patch clamp technique, where the pipette solution faces the extracellular side of the channel and the bath solution faces the intracellular side. Excised patches contained one to about fifty maxi-K channels. Maxi-K channels were identified by their large single channel conductance (250-300 pS), and by sensitivity of channel gating to membrane potential and intracellular calcium concentration. Membrane currents were recorded using standard electrophysiological techniques. Glass pipettes (Garner 7052) were pulled in two stages with a Kopf puller (model 750), and electrode resistance was 1-3 megohms when filled with saline. Membrane currents were recorded with EPC9 (HEKA Instruments) or Axopatch 1D (Axon Instruments) amplifiers, and digital conversion was done with ITC-16 interfaces (Instrutech Corp). Pipettes were filled with (mM); 150 KCl, 10 Hepes, 1 $MgCl_2$, 0.01 $CaCl_2$, 3.65 KOH, pH 7.20. The bath (intracellular) solution was identical, except, in some cases, calcium was removed, 1 mM EGTA was added and 20 mM KCl was replaced with 20 mM KF to eliminate calcium to test for calcium sensitivity of channel gating. Drugs were applied to the intracellular side of the channel by bath perfusion.

Human non-pigmented ciliary epithelial cells were grown in tissue culture as described (Martin-Vasallo, P., Ghosh, S., and Coca-Prados, M., 1989, J. Cell. Physiol. 141, 243-252), and plated onto glass cover slips prior to use. High resistance seals (>1 Gohm) were formed between the pipette and cell surface, and inside out patches were excised. Maxi-K channels in the patch were identified by their gating properties; channel open probability increased in response to membrane depolarization and elevated intracellular calcium. In patches used for pharmacological analysis, removing intracellular calcium eliminated voltage-gated currents. Maxi-K currents were measured after depolarizing voltage steps or ramps that caused channel opening.

The compounds of this invention were applied to the intracellular side of the channel in appropriate concentrations (0.001 to 100 μM). The compounds reduced channel open probability, and this effect was reversed upon washout of compounds from the experimental chamber. The IC50 for block of maxi-K channels under these conditions for the compounds of this invention ranged from about 0.5 nM to about 10 μM.